



# MEDICINE

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## HYPERPLASIA OF LYMPHOID TISSUE AND LYMPHOCYTOSIS

CAROLINE WHITNEY

*From the Henry Phipps Institute, University of Pennsylvania, Philadelphia, Pennsylvania*

The functions of the lymphocyte, which are intimately concerned with many physiological processes have not, as yet, been clearly defined

It is maintained that the lymphocyte is a stem cell capable of wide differentiation, Maximow (1907, 1917, 1923) and Weidenreich (1911), Dominici (1902, 1909, 1920), Jordan (1926a, 1926b) and others claim that a basophilic mononuclear cell which they identify with the lymphocyte is capable of giving rise to all other types of definitive blood cells Other authors, Cunningham, Sabin, and Doan (1925a, 1925b), Naegeli (1922), etc., think that the erythrocyte, unlike the lymphocyte, arises within the blood vessels from the endothelium, the first stage in its development being the megaloblast, which is basophilic like the lymphocyte but not identical with it

Enormous numbers of lymphocytes, many more than are present in the blood at any one time, leave the circulation daily Bunting and Huston (1921) calculated from Rous' data on dogs that there is a daily output of 3,300,000,000 lymphocytes from the thoracic duct Experiments to determine the fate of these lymphocytes have led to speculation concerning their function Bunting and Huston (1921) judge from their histological studies of the lymphocytes in the intestinal wall that the daily exit of lymphocytes takes place there They feel that one of the functions of the lymphocyte is there fulfilled and they hazard the opinion that there may be some relation between the lymphocyte and the countless bacteria and their toxins found in the intestinal wall

Jordan and Sperdel (1923, 1924), who believe that the lymphocyte is pluripotential and capable of generating all types of blood cells, suggest that this excess of lymphocytes filters out in the bone marrow

where these cells act as progenitors of blood cells both red and white. They confirm the evidence offered by Bunting and Huston to prove that many lymphocytes are lost in the intestine. In the agminated follicles the lymphocyte may have an antitoxic as well as phagocytic and digestive function.

The lymphocyte seems to be associated in some way with resistance, for it has been repeatedly observed that as a disease overcomes the resistance of its host the lymphocyte count drops. This statement has been made not only in reference to tuberculosis but also to measles, smallpox, acute infections in children and other diseases. Experimentally Murphy and Sturm (1919b) found evidence that resistance to tuberculosis was lowered when the lymphoid tissue of guinea pigs was decreased by the use of x-ray. They also found heightened resistance to tuberculosis following splenectomy when, as is well known, the lymphocytes of the blood show a definite increase. Sabin (1926) suggested that a high lymphocyte count in an animal means good resistance to tuberculosis. Amoss, Taylor, and Witherbee (1919) tried to establish some positive evidence that resistance to poliomyelitis was influenced by the number of lymphocytes, they found a decreased resistance in those animals which had been deprived of lymphoid tissue by x-ray, but they could not prove to their entire satisfaction that there was no other contributory factor.

Many investigators have noticed the collection of lymphocytes about slowly growing cancer and have speculated upon the relation of the lymphocyte to cancer immunity. Da Fano (1910) called attention to an accumulation of lymphocytes in the subcutaneous tissues of animals which were apparently resistant to cancer transplants. Murphy and Morton (1918) found a higher number of these cells in the circulating blood of resistant animals, likewise they could render mice of tested immunity susceptible to inoculation with cancer transplants by destroying the lymphoid tissue with x-ray. Murphy and Nakahara (1920) found in animals made resistant to cancer that there was active proliferation of cells in the lymphoid organs following cancer inoculation. Loeb (1926) uses the lymphocytic response to transplanted tissue as a fine method of measuring the individual immunity to tumor growths. Sittenfeld (1912, 1918), on the other hand, could not heighten the immunity of his animals to tumor transplants by increasing their lymphoid tissue.

In tissue culture work Carrel (1923) has shown that the lymphocytes are capable of living upon serum alone and of manufacturing therefrom a substance which other cells can utilize. All other cells remain inactive in serum for they require something found in embryonic tissue extract for their life and growth. However, if lymphocytes are added to such a culture the other cells begin to grow and divide in the usual way.

This function of the lymphocytes *in vitro* is the only one which has been proven experimentally. It is obvious that much work has yet to be done before the function of the lymphocytes *in vivo* is fully defined, the part played by them in resistance to infectious diseases and to cancer is not clear, and whether they are the progenitors of all other definitive blood cells is still debatable.

#### AGE CHANGES IN LYMPHOID TISSUE

In growing animals lymphatic tissue is abundant and lymphocytes form a large part of the leucocytes of the blood, but with increasing age there is a decrease in the amount of lymphoid tissue which is more than can be accounted for by the general tissue atrophy of old age. The embryology of lymphatic tissue has been investigated by numerous workers, among the more recent Lewis (1906), Sabin (1902, 1908, 1909), Clark and Clark (1920), and Huntington and McClure (1908) and Huntington (1910, 1914). There is still some controversy over the exact picture in each stage of development of the lymph vessels but there is general agreement as to the extent of lymphatic tissue and the time of its first appearance. The lymph vessels are first seen in the human embryo of about 10 mm length near the jugular vein (Lewis, 1909). Buds from the jugular lymph sac grow and form at least the proximal part of the numerous and voluminous lymph channels which soon appear in the head, neck and thorax. The abdominal lymph vessels develop later (20-mm embryo). In the rabbit the first lymph nodes appear at about twenty days (29-mm embryo) (Lewis, 1909). The developing lymph node (Sabin, 1909) is at first merely a thickening of the connective tissue about lymph vessels, lymphocytes collect in this region while the lymph ducts multiply and become sinuses. The growth of lymphoid tissue is then rapid and the lymphatic system of the fetus becomes extensive.



Observations of the post-fetal changes in the character and amount of lymphoid tissue are not recorded until the eighteenth century, although lymph and the lymphatic system were recognized by Aristotle, Erasistratus and Herophilus. Among the earliest to remark these changes were Malpighi, in 1666, Haller, in 1765, Ludwig, in 1789, and Bichat, in 1801. Breschet (1836) found the lymph nodes softer and more voluminous in infants and young people than in adults, and observed apparent atrophy in old age. From that time on there are frequent comments upon the variations in the size of the lymph nodes, the lymphoid tissue in the intestine, the thymus, the tonsils, etc.

Gray (1859)

The Malpighian bodies (of the spleen) may be observed in the healthy organ at all periods of life but they are larger and more distinct in early than in adult life or old age. The size may vary at the same period of life at different times and under different circumstances but their number as well as their size seems to be far greater in proportion to the size of the organ in early than in adult life.

Sappey (1868):

The dimensions (of the appendix) are not influenced by the development of the rest of the intestine. The development of the vermicular appendix is almost completely achieved at birth, and its definitive state is reached in the new born. It ceases to grow almost completely from the cessation of intra-uterine life.

Morris (1921)

The thymus follows the typical course of a lymphoid organ. At birth it forms about 0.42 per cent of the body weight. The relative weight drops to 0.09 per cent in adolescence and 0.05 to 0.02 per cent in early maturity. The absolute weight rises from about 13 grains at birth to 38 grains at puberty, then declines. After birth the parenchyma forms a constantly decreasing proportion of the thymus.

These are a few of the numerous comments on the course of lymphoid tissue as it is observed in the autopsy room and anatomy room. Although the thymus has been included here with lymphoid

organs, the exact classification of this gland is yet to be made, for authorities disagree as to the origin of the small thymus cell and some question its identity with the lymphocyte Pappenheimer (1910) says "It is possible to demonstrate slight morphological differences between small thymus cells and the true lymphocyte found in lymph nodes although they are so slight as to make absolute differentiation by the usual methods oftentimes impossible" He agrees with Stohr and Bell that the small thymus cell is of epithelial origin The opposite view is held by His, Stieda, Dohrn and Gulland, who believe that the thymus cell has a mesodermal origin and is identical with

TABLE 1  
*The quantity of lymph tissue per kilogram of body weight*

AGE	LYMPH NODES				LYMPH TISSUE IN			
	Scapular	Inguinal	Neck	Popliteal	Tonsils	Spleen	Appendix	Peyer's plaques
1 month	0 049	0 030	0 26	0 118	0 027	0 106	1 61	0 032
2 months	0 052	0 030	0 23	0 124	0 032	0 092	2 08	0 112
3 months	0 078	0 041	0 25	0 126	0 026	0 079	2 11	0 147
4 months	0 096	0 049	0 26	0 135	0 029	0 084	2 15	0 143
5 months	0 098	0 054	0 26	0 132	0 021	0 076	2 31	0 133
6 months	0 087	0 044	0 25	0 115	0 024	0 082	2 19	0 135
7½ months	0 076	0 046	0 24	0 106	0 022	0 061	1 94	0 082
10 months	0 072	0 038	0 23	0 124	0 031	0 054	2 52	0 087
12 months	0 061	0 035	0 21	0 116	0 022	0 054	2 19	0 084
2 years	0 058	0 034	0 20	0 098	0 021	0 048	1 67	0 073
3½ years	0 044	0 025	0 15	0 076	0 023	0 057	1 19	0 062

the lymphocyte In text books of histology (Hill, 1923, Jordan, 1924, Mottram, 1923) the thymus is classed as a lymphoid organ with the qualifying statement that its real nature is under discussion

T J Hellman (1913) made a study of the development and involution of lymphatic tissue in a series of healthy rabbits which had been killed instantaneously He found very little individual variation in the amount of lymphoid tissue and no difference in its distribution in the two sexes The various types of lymphoid tissue did not proceed to grow at the same rate but the increase and decrease of lymphoid tissue in general were slightly greater than that of the organs Cervical and popliteal lymph nodes increased until the twelfth month

and then showed a steady decline. The other lymph nodes grew in size only until the fifth month (the time of sexual maturity in the rabbit), and then began their involution. The lymphoid tissue of the intestine increased until the fifth month, remained at the same level until the seventh month, developed vigorously until the tenth month, then gradually declined. The spleen increased until the fifth month and thereafter showed slight but steady involution. The pharyngeal tonsils increased until the fifth month, remained the same until the tenth month and then atrophied. The maximal proportion of lymphoid tissue to body weight in general is greatest between the second and fifth months. Lymphoid tissue, then, reaches the peak of development at the time that the animal attains sexual maturity. Table 1 records the relative weights of the various lymphoid organs in succeeding months.

Parallel with the gross changes in the lymphoid organs there are, of course, changes in the microscopic structure. Luther West (1924) studied sections from the cecum of rats, cats and rabbits of various ages from early youth to extreme age. The cecum in the young animals showed abundant lymphoid tissue, the nodules being closely packed, and of such bulk that they filled one third of the lumen. Surrounding the nodule in the connective tissue were numerous eosinophiles. On the surface of the nodule blood and lymph vessels were abundant. The small lymphocyte was the predominating cell in this region. In the germinal center were large lighter staining cells with many cytoplasmic inclusions. Here were many mitotic figures. Blood vessels were few and small. In very old animals on the other hand, there were no definite nodules. Occasional accumulations of lymphocytes seemed to indicate the site of former nodules. The small lymphocyte predominated. There was no germinal center and the nodule was of the same density throughout. The connective tissue looked "as if there had been a collapse of a one-time distended region." The animals of ages between extreme youth and senility showed the intermediate stages of atrophy. Curiously, the regression did not in every case correspond with chronological age, but seemed to depend somewhat on the general physical condition, a poor condition induced more rapid atrophy.

The decreasing amount of lymphoid tissue in the body as a whole

is accompanied, until near puberty, by a decreasing number of lymphocytes in the blood stream. There is in infancy both an absolutely and relatively high count of lymph cells, the total leucocyte count being two or three times the number in adult blood. In childhood the total count, though less than in infancy is still above that of the adult. The percentage of lymphocytes, at first 50 to 70 per cent and sometimes as high as 80 per cent, decreases gradually to about 36 per cent at the age of ten. Such observations may be found in any textbook of medicine, pediatrics, or hematology in which the normal blood picture is discussed. See Da Costa (1901), Erlich (1905), Todd (1908), Naegeli (1922), Holt (1922), Schilling (1926).

#### CLINICAL OBSERVATIONS ON LYMPHOCYTES

Children often respond with a lymphocytosis to any acute infection. Gulland and Goodall (1912) say that in general the total number of leucocytes responds more readily in children to any toxic stimulus and that the proportion of lymphocytes always tends to be greater than in adults in a corresponding condition. Stettner (1925) after studying many cases, says that an increase in the total white count with a very high percentage of lymphocytes is characteristic of many acute infections in children which are not overwhelming. However, if the child's resistance is poor the percentage of polymorphonuclear cells tends to rise.

A similar lymphocytic response to acute infections is not unknown in adults. Naegeli (1922) and Erlich (1905) mention its occurrence. Turk (1911) considers it a key to the understanding of acute leucemias. Cabot (1913) cites a case of wound sepsis with a total leucocyte count of 20,000 in which "the percentage of lymphocytes did not rise above 70 per cent." Agun, a case of boils showed a total white count of 16,400, 86 per cent of which were lymphocytes. A third case was of widespread streptococcal infection of tonsillar origin with a total white count of 9000, of which 71 per cent were lymphocytes. All of these patients recovered and eventually showed a normal blood picture. Elsewhere Cabot (1904) reports a case of pneumonia with a total white count of 94,600, 69 per cent being lymphocytes. C. C. Cole (1916) instances a case of infection of the lymph nodes with bacillus paratyphosus in which, with a total white count of 10,400, 46.7 per cent

were lymphocytes and 14.75 per cent large mononuclears. The patient was discharged from the hospital one year after the onset of his symptoms showing "some improvement." Other blood counts are not reported.

Krumbhaar (1926) reports 10 cases with leucemoid blood pictures. Of these, 2 showed a lymphocytosis in response to acute infection. His first case, however, is a child of three years with measles and pertussis presenting a leucocytosis of 71,000 with 82 per cent lymphocytes. Such a picture is not unusual in a child with that disease. The second is an adult with post-partum pyelitis. The first day of the disease she showed a total leucocyte count of 7600, 75 per cent of which were lymphocytes. The second day with 8500 leucocytes, 30 per cent were lymphocytes. The sixth day, of 15,000 leucocytes only 25 per cent were lymphocytes.

Daland (1921) analyzed 100 cases of periapical dental infection in adults and found that 54 had a lymphocytosis of over 30 per cent. This was a relative rather than an absolute increase in lymph cells, for the total leucocyte count was normal or decreased, averaging 5800. Of the 54, the average percentage of lymph cells (chiefly small lymphocytes) was 40, while 62 per cent was the maximum figure.

Among the earlier cases cited as examples of a lymphocytic response to acute infections are many of the now fairly well-defined disease called infectious mononucleosis in which the characteristic cell is a mononuclear very similar to the lymphocyte. In size, this cell is intermediate between the small and large lymphocytes. Careful study has shown that it has a number of characteristics which distinguish it from the normal cell (Sprunt and Evans, 1920, Bloedorn and Houghton, 1921, Longcope, 1922, Cottrell, 1927). In the majority of the reports of this disease, however, these cells are classed as lymphocytes and differential counts show an actual and relative "lymphocytosis" as high as 75 per cent in some cases, with a total leucocyte count varying between 6000 and 40,000.

There are certain diseases, excluding leukemia, that are regularly attended by a lymphocytosis, which have been widely discussed in the literature, namely whooping cough, tuberculosis, smallpox, etc.

In pertussis it has been ascertained that the average leucocyte count is about 25,000, 40 to 60 per cent being lymph cells. In uncomplicated

pertussis the count sometimes rises as high as eighty or ninety thousand and Seitz (1925), in his review of the literature on the subject, finds that 8 cases with a total leucocyte count of 100,000 were reported during 1925 Churchill (1906) found 93 per cent lymph cells in the blood picture during the catarrhal stage When pertussis is complicated by pneumonia the count may rise to a tremendous number and the blood picture may closely resemble lymphatic leucemia Cabot (1904) cites a case of pertussis-pneumonia in which there was a total leucocyte count of 227,870, 50 per cent of which were lymphocytes Crombie (1908) found a count of 233,000, with 58 per cent lymph cells, in his case of pertussis pneumonia

The blood picture in smallpox varies with the stage of the disease but from the onset there is a relative if not an absolute lymphocytosis In the earliest stages there is a normal or decreased number of leucocytes but the percentage of lymphocytes may be as high as 60 per cent Hoffman (1923a, 1923b) states that from the fourth day there is a leucocytosis of 17,000 to 30,000 or even higher, and his observations are confirmed by other writers The leucocyte count reaches its highest figure on the ninth to fourteenth day and may remain as high as 24,000, during the whole third week In the fourth, fifth and sixth weeks the count is about 9000 to 12,000 The lymphocytes show a striking increase above normal and may reach 65 or 75 per cent in the third week This condition may persist through the sixth week after the onset of the disease According to Courmont and Barbaroux (1900) those patients who showed a low lymphocyte percentage usually died If there are complications they are characterized by a neutrophilic leucocytosis

It has been proved both clinically and experimentally that those instances of tuberculosis in which there is strong resistance, show an increase in the percentage of lymphocytes Calmette (1922) says that with benign fibroid tuberculosis there may be a moderate leucocytosis, not over 10,000, and that this increase is largely confined to the lymph cells In a patient with a massive infection whose defense is being broken down there is a leucocytosis with a diminishing percentage of lymphocytes In open progressive tuberculosis with cavities and caseation the count may be 10,000 to 20,000, 90 per cent being polymorphonuclears Bergel (1913) says that a high lympho-

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cyte count means an unmixed tuberculous infection with a favorable prognosis. Wright and King (1911) analyzed 577 cases of tuberculosis and found that those with a high lymphocyte count invariably improved and that a decreasing number of lymph cells accompanied a decreasing resistance to the infection. Watkins' (1911) counts on patients at Phoenix showed that of 13 patients actually cured the percentage of lymphocytes varied from 45 to 67 per cent, and of 44 patients showing rapidly progressing lesions the average percentage of lymphocytes was 25. The figures obtained by Webb, Newman and Gilbert (1922-23) and by Webb and Williams (1909) correspond well with those of Watkins.

The effect of tuberculosis on the blood picture of rabbits has been carefully studied by Sabin (1926). She says, "There is an increase in the percentage and in the actual number of monocytes after infection with tuberculosis and the average percentage of lymphocytes remains the same, with, however, a slight decrease in their number." She found the normal ratio of monocytes to lymphocytes 1 to 2.97. In cases in which there was a favorable reaction to the infection the ratio was 1 to 3.56. In cases in which the reaction was unfavorable the ratio was 1 to 0.79. When the lymphocytes were consistently higher than the monocytes even though the actual number of monocytes was above normal she found "arrested tuberculosis without exception."

Downing, Allison and Woodman (1918) present ten instances of pneumothorax in tuberculous patients in all of whom the differential counts taken after operation showed an increase in lymphocytes of 10 to 25 per cent over the count previous to operation.

Findlay (1920) observes that in pellagra there is an increase in the lymphocytes of the blood very early in the disease. It may precede the appearance of skin lesion. Eighty per cent of his cases showed a lymphocytosis of over 30 per cent. The highest percentage was 69. The total leucocyte count was slightly increased.

Any disease which produces a leucopenia may also produce a relative lymphocytosis for the diminution seems to be at the expense of the polymorphonuclear cells. In this group are included influenza, typhoid fever, chicken pox, pernicious anemia and various endocrine disorders.

In influenza there is early an absolute reduction in the number of lymph cells, 16 to 20 per cent. Later the reduction in the number of neutrophils is more rapid and the lymphocyte percentage is relatively high. According to Bunting (1921) there may be an absolute increase in the number of lymphocytes although there is usually a low leucocyte count.

The lymphocytosis of typhoid fever, also relative, may be as high as 46 per cent. Its onset is simultaneous with the appearance of the leucopenia and it progresses with the leucopenia to the fourth, fifth and sixth week of the disease. This reaction in typhoid fever has been discussed by Ewing (1903), Buchannan (1909), Dieulafoi (1910), Sahlh (1911), Hultgen (1911), etc.

In chicken pox the lymph cells greatly exceed the neutrophils, there may be an actual increase in the number of lymphocytes although the total leucocyte count be lowered. The following figures by Pantosis (1924) represent the usual course of the leucocyte count throughout the disease.

	ONSET	PRODROMAL	PREERUPTIVE	ERUPTION
Total	9,000	4,000	3,700	7,800
Lymphocytes	1,500	3,000	1,700	3,800

In the prodromal and early eruptive stages of measles there is usually a leucopenia with a relative lymphocytosis which persists during convalescence (Usbeck, 1923). Occasionally there is an absolute as well as relative lymphocytosis but such cases are rare.

In mumps there is a leucopenia and a relative lymphocytosis which is particularly marked in the late stages (Feiling, 1913).

Of pernicious anemia, Ehrlich (1905) says that the lymph cells show a regular increase in percentage which may be as high as 63 per cent. The total white count is low.

Reider (1892) analyzed 12 cases of chlorosis and found on an average 33 per cent lymphocytes although some showed as much as 55 per cent lymph cells.

Falta (1923) found in exophthalmic goiter and myxedema a leucopenia with a relative lymphocytosis of 40 to 50 per cent. In speaking of sporadic cretinism, he says, "There may be an enormous reduction

in the polymorphonuclear leucocyte count and a corresponding increase in the lymphocytes even when we consider that in children the number of neutrophils is smaller than in adults" In "multiple gland sclerosis" in which many of the ductless glands showed a somewhat pathological picture, he found not a leucopenia, but a mild leucocytosis with the increase formed by mononuclear cells and eosinophiles Borchardt (1912) cites one instance of exophthalmic goiter in which the blood picture showed 69 per cent lymphocytes These pictures are similar to those reported by Gordon and von Jagic (1908)

According to Perry (1896) feeding thyroid gland produces a relative lymphocytosis He fed a number of insane patients 30 to 50 grains thyroid gland daily Total leucocyte counts and differential counts were made before the institution of treatment, during treatment, and in some cases for a short time after its discontinuance In every case there was a decided relative increase in the lymphoid cells with no change in the total leucocyte count Some of the cases presented a very low initial count and in these, although there was a definite increase in the lymphocytes, the ultimate amount was not above normal As an example, case IV had an initial count of 8200 with 10.8 per cent small lymphocytes and 3.6 per cent large lymphocytes The patient was fed 40 grains of thyroid gland daily On the third day the differential count showed 20.7 per cent small lymphocytes and 4.0 per cent large lymphocytes In other cases the small lymphocytes reached 55 per cent, the preliminary count having been 30 to 31 per cent small lymphocytes In case V the relative lymphocytosis induced by the feeding of 31 grains of thyroid daily persisted throughout ten days of freedom from treatment

Many tropical fevers, kala azar (Rogers, 1919), dengue (Rogers, 1919, Vedder, 1907), typhus (Rogers, 1919), and trypanosomiasis (Rogers, 1919) are characterized by a leucopenia with a relative lymphocytosis In malaria (Vincent, 1897, Stephens and Christopher, 1899-1902, and Rogers, 1919) there is usually a relative increase in the large mononuclear cells with occasionally an increase in the lymphocytes If the case be one in which there are very large numbers of parasites the increase may be not only relative but absolute since in such cases the total white count may rise as high as 20,000 In

Malta fever, also, there is an absolute lymphocytosis (Rogers, 1919)

In syphilis (Hazen, 1913) the blood picture varies with the stage of the disease and treatment. In untreated secondary lues the total leucocyte count may be as high as 20,000 with the increase due to polymorphonuclear cells. With treatment the total cell count drops and the lymphocyte percentage rises, the average being 42 per cent in cases with a papular eruption. In untreated tertiary syphilis the total cell count and the differential is usually normal, but with treatment the percentage of lymphocytes rises.

There are leucopenias other than those produced by disease which have a relative lymphocytosis. Widal's (Widal, Abram and Iancovesco, 1920) hemoclastic crisis (which consists of a sharp drop in the leucocyte count following ingestion of 200 cc of milk in cases of hepatic insufficiency) is a leucopenia with a relative lymphocytosis. It has been described as an "exode leucocytaire" for there is a sudden drop in the number of polymorphonuclear cells while the lymphocytes remain in the blood stream in the same numbers. This hemoclastic crisis is said to be normal in young infants following the ingestion of food (Dorlencourt, Banu et Paychere, 1921). However in these cases there is no actual increase in the number of lymph cells in the blood stream. Garrelton and Santenois (1921) produced an actual increase in the lymphocytes following the injection of peptone and pilocarpine, but their figures as to the effect of the shock so produced are of no value because pilocarpine alone brings about an increase in lymph cells. The "choc hemoclastic" produced by Tinel and Santenois (1921) and Tinel (1923) with the oculocardiac reflex (vagal stimulation brought about by firm pressure on the eyeballs) is another example of a relative lymphocytosis with leucopenia.

#### RELATION OF THE LYMPHOCYTE TO DIGESTION AND NUTRITION

The leucocytosis which follows the ingestion of food is well known and it is generally agreed that the maximum rise in the total leucocyte count (it may double the original number) occurs two or three hours after a meal. Pagniez and Pichet (1923) obtained the following results in their differential counts of blood in patients after ingestion of a standard meal.

	TOTAL	NEUTROPHILES	LYMPHOCYTES
Before	5,500	3,500	2,000
2 hours after meal (maximum rise)	7,500	4,500	3,000

The results in 9 other patients were similar. The neutrophiles and lymphocytes rise together. These observations correspond to those of Reider (1892) and of Da Costa (1901). Brodin and St Girons (1918) find the increase in total count due almost altogether to polymorphonuclear cells. Émile-Weil (1920) maintains that although the initial leucocytosis may be characterized chiefly by neutrophiles, there is a "lymphocytose digestive tardive" which occurs about seven hours after ingestion of food. This late rise is a true digestive lymphocytosis which may amount to 40 per cent. He examined microscopic sections of the intestine of cat, rabbit, pig and rat during the process of digestion and found an apparent increase in lymphoid tissue with an abundance of lymphocytes in the intestinal wall during digestion.

The kind of diet on which an animal lives has a definite influence on the amount of lymphoid tissue present in the body but it has no relation to the blood picture. Czerney (1907) finds some association between the amount of body fat and the amount of lymphoid tissue. Settles (1921) carried on experiments on kittens to determine the effect of high fat diet. He found that in kittens receiving a large amount of fat the lymphoid tissue was noticeably greater than in kittens on a low fat diet. Lefholtz (1923) carried the experiments further to determine the effect of a high caloric diet of any variety, protein, carbohydrate or fat supplying the excess calories. He found that the size of the cervical lymph nodes, the thymus, and the spleen had no relation to diet. The mesenteric nodes and the pharyngeal and palatine tonsils were decidedly larger in animals on high fat diet while the high caloric diet of any variety produced a much larger amount of lymphoid tissue than a normal diet. The lymphoid tissue of the buccopharyngeal cavity and intestines was apparently regulated by the caloric intake and specifically influenced by the fat content of the diet.

Clark and Clark's experiment (1917), in which they injected fat droplets into a tadpole's tail and watched the cellular reaction which followed, shows that fat has a special attraction for the lym-

phocyte The droplets were surrounded by a circle of lymphocytes after injection, the polymorphonuclear cells were much slower in accumulating Branching lymphoid vessels could be seen pushing out toward the fat It did not take long for the droplets to be completely absorbed

#### LYMPHOCYTES AFTER SPLENECTOMY

Splenectomy is regularly followed by an increase of lymph cells in the blood Kurloff (1888) found a gradual and progressive increase of the blood lymphocytes which doubled and tripled their number in the course of a year or two after splenectomy The number of other cellular elements in the blood was practically unchanged He also found that the hypertrophy and hyperplasia of the lymph nodes, especially of the mesentery, which develops after the operation occurs very frequently Of the duration of the blood lymphocytosis he says, "The condition of lymphemia may persist exceptionally for years, although in the majority of cases it retrogrades during the course of the first year even to a condition in which a smaller number of lymphocytes than normal is produced" His observations have been confirmed by numerous workers since his time Matthew and Miles (1907) following the course of the blood picture after excision of the spleen for traumatic rupture obtained the following results

DATE	TOTAL COUNT	LYMPHOCYTES
		<i>per cent</i>
February 6, 1905	Operation 24,000 10,000 8,500	
February 9, 1905		16
January, 1906		58
April, 1907		59

They also observed enlargement of the lymph nodes following the operation but they remark that it is not great and not permanent Roughton, Leg and Emery (1907) found similar blood pictures

Hall (1920) claimed that there were three periods following splenectomy, each with a characteristic blood picture He cites a case in which a splenectomy was performed in August The first period was of one month's duration and in that time all of the cells were



equally increased During the second period (September and October) there was a marked variation in all the leucocytes, but in the third period (November) there was a slight leucocytosis (average 11,570) entirely due to the lymphocytes (39.5 per cent) He does not follow the case beyond the fourth post-operative month

Pearce, Krumbhaar and Frazier (1918) found an initial polymorphonuclear leucocytosis with a late slight increase in lymphocytes following splenectomy They made a particular study of the bone marrow and lymph nodes in dogs and found a hyperplasia shortly after operation, however, it was of short duration and no new formation whatsoever was observed in late periods after the operation In contrast to the observations of Tizzoni (1882), Mosler (1884) and Warthin (1902) no new formation of hemolymph nodes was noticed They found hyperplasia of the bone marrow several months after the operation but it did not involve the lymphoid cells more than any of the other bone marrow constituents In a monkey which had undergone splenectomy, partial myelotomy and nodectomy two years previously and which had received injections of camphorated oil shortly afterward, Krumbhaar (1922) found the bone marrow studded with lymphoid follicles The number of experimental procedures to which the animal had been subjected made it impossible to assign a definite cause for the metaplasia

In general the opinion seems to be that following splenectomy there is a late lymphocytosis in the blood appearing four months to one year after the operation and persisting two or three years There is a slight initial enlargement of the lymph nodes but it does not persist There is little if any increase in the lymphoid elements in the bone marrow

#### EXPERIMENTAL PRODUCTION OF LYMPHOCYTOSIS

Exposure to dry heat provokes an extreme and enduring increase in the lymph cells in the blood and an increase in lymphoid tissue in the body The work on blood counts in tropical countries will be taken up under the effect of sunlight, for although the heat of the sun may play a part in raising the percentage of lymphocytes, the light of the sun may be equally important Murphy and Sturm (1919a) exposed mice to dry heat at 55° to 65°C. for five minutes and

found that there was a distinct fall in the white count immediately after exposure. Both neutrophiles and lymphocytes were involved in the decrease. The neutrophiles, however, recovered slowly while the lymphocytes increased so rapidly that by the second week after heating the count often reached a point 200 to 300 per cent above normal. The large lymphocytes predominated in the early stages and the small lymphocytes in the later stages of recovery. Waro Nakahara (1919), investigating the source of these mononuclears, came to the conclusion that actual proliferation of the lymphoid tissue gave rise to the increase in lymph cells in the blood. He found that the spleen showed a certain amount of necrosis outside the germinal center immediately after exposure to heat but there was no change, at this time, in the germinal center itself. Forty-eight hours later there was more marked necrosis but the germinal center had become very active. On the fourth day necrosis was rapidly disappearing and the germinal center was still showing activity. The picture in the lymph nodes closely resembled that in the spleen.

The effect of sunlight on the blood count of people of the tropical countries has been the subject of special investigation by Wickline (1908), Phalen (1910), and Chamberlain and Vedder (1911). All found a lymphocyte increase which was relative only. The total leucocyte count remains the same while the percentage of neutrophiles decreases as the lymphocyte percentage rises. Wickline took blood counts of soldiers recently arrived in the tropics, December, 1905. The average lymphocyte percentage at that time was 23.8 per cent. Two years later, April, 1907, the average percentage had risen to 34. The total leucocyte count remained the same. Phalen's observations corroborate these findings. He made the additional observation that the lymphocyte percentage was slightly higher in blondes (33 per cent) than in brunettes (29 per cent).

Taylor (1919) made blood studies of individuals who had been exposed to sunlight at Woods Hole and who had acquired a tan over the greater part of their bodies. Those of his group, namely, 25 per cent, who showed a definite increase in lymphocytes were all tanned to a greater or less extent. Those who showed no increase in lymphocytes were of a pasty type who never tan.

Janet Clark (1921) tried the effect of light rays of varying wave

length from various sources upon guinea pigs With the bare iron arc (wave length of  $238\mu\mu$  and above) she found a normal polymorphonuclear count, and, except for an initial drop immediately after exposure, a lymphocyte count above normal during three weeks The maximum rise on the fifth day, amounted to over 100 per cent over the original count When the light was passed through a glass screen transmitting wave lengths of  $320\mu\mu$  and above, the total count remained unchanged immediately after exposure, although there was a fall of lymphocytes balanced by an increase in polymorphonuclear cells Three days after exposure the total count dropped and remained low until the fourteenth day, after which there was a gradual return to the original count All filters which cut out the wave lengths from  $280\mu\mu$  to  $320$ , the so-called "far ultra-violet" light, caused a decrease in lymphocytes Only those filters which permitted the passage of the far ultra-violet would produce a lymphocytosis The total effect of sunlight, according to Clark, is usually a balance between the effect of those rays which stimulate lymphocyte production and those which depress it Repeated irradiation had no greater result than a single exposure In these experiments the effect of heat was excluded

Thomas, Taylor and Witherbee (1919), Murphy and Morton (1918), Sittenfield (1918), Murphy and Nakahara (1920), Nakahara and Murphy (1922) have produced an equally definite and lasting lymphocytosis by the use of x-ray in small doses Large doses produce definite destruction of lymphoid tissue, but with properly regulated technique the lymphocytes (in mice) increase from 4000 to 6000 lymph cells per cubic millimeter (2000 cells increase) This increase occurs in from four to fourteen days after exposure and persists during two or three weeks There is an initial lymphopenia immediately following x-ray exposure, just as there is following a dry heat exposure Nakahara (1919) found that the blood picture induced by dry heat and that induced by x-ray were indistinguishable, but the microscopic changes in the lymph nodes and spleen were somewhat different Necrosis was seldom seen and mitotic figures in the germinal centers were numerous The stimulating effect appeared immediately after treatment and became more evident in two or three days It persisted in slight degree until the fourteenth day He believes that the

lymphocytosis caused by x-ray is due to a primary stimulative effect of the agent, and hence is fundamentally different from the similar lymphocytosis induced by heat which is a regenerative phenomenon

That altitude has an effect on the leucocyte picture has been asserted by many authors. Staines, James and Rosenberg (1914) took differential counts of medical students and monkeys in New York City and at an altitude of 6000 feet in Colorado, and they say in conclusion "It is certainly safe to say that at an elevation of 6000 feet the larger lymphocytes are absolutely increased in the circulating blood by about 20 to 30 per cent in both men and monkeys." The total leucocyte count was the same at both levels. Webb and Williams (1909), and Staubli (1910), Baer and Englesman (1913) also found a very definite increase in the percentage of lymphocytes at higher altitudes. Gilbert's (1911) counts were taken at various altitudes, from below sea level in the Salton Sink, California, to 9000 feet at Ward, Colorado. He found at each of these points a lymphocyte percentage of 38 to 43 per cent. His opinion is that perhaps the altitude alone is not responsible for the high percentage of lymphocytes, but that the amount of sunshine in such places as Phoenix, Arizona, or Salton Sink may be a factor.

An increase in the lymphocytes of the circulating blood may be brought about in other ways than by increasing the total number of lymphocytes in the body, lymph cells may be forced into the circulation from the various lymphatic depots such as spleen and lymph nodes, by mechanical pressure or by increasing the volume flow of lymph through these organs.

Contraction of the smooth muscle in spleen and lymph nodes by means of various drugs mechanically forces lymphocytes into the blood stream. The production of lymphocytosis by drugs was attempted by Horbaczewski (1891) and by Ruzicka (1893). Harvey (1906) tried pilocarpine as well as barium chloride, muscarine and adrenalin. Before and after injection of these drugs into the ear vein of a dog, cat and rabbit, he made total and differential leucocyte counts and obtained the results shown in table on page 20.

It was his opinion that the lymphocytosis was produced by contraction of the plain muscle in spleen and lymph nodes.

	TOTAL LEUCOCYTE COUNT		PERCENTAGE OF LYMPHOCYTES	
	Before	After	Before <i>per cent</i>	After <i>per cent</i>
Pilocarpine, 0.001 gram	5,866	9,733	43	66
Muscarine, 0.5 cc	12,800	17,200	33	45
Barium chloride, 0.01 gram	10,600	12,233	36	52
Adrenalin, 3 cc 1 per cent solution	7,000	6,200	37	74

Peyton Rous (1908) collected lymph as it dropped from a cannula in the thoracic duct following injection of pilocarpine and following muscular activity. The lymph was mixed with equal parts of citrate solution and counts were made of the cells it contained. He found that during muscular activity the output of cells from the thoracic duct, mostly lymphocytes, was tripled or quadrupled. There was an increase in volume flow as well as in cellular content. Pilocarpine also caused a rise in the number of cells. The effect is due, he thinks, to contraction of the smooth muscle in spleen and lymph nodes. He also gave glucose solution intravenously, and although the individual drops of lymph were poor in cells, the whole output was very large and suggested that the total blood count might be increased.

R. L. Dixon (1912) demonstrated that vigorous massage of the spleen would cause an increase in the lymphocytes of the thoracic duct. The increase in mononuclears of the thoracic duct lymph following injection of pilocarpine with splenectomized animals he attributes to the mechanical action of the heightened activity of the respiratory organs and the intestine.

Lee (1922, 1924) found that the rise in the number of lymphocytes in the general circulation following pilocarpine was unchanged by ligation of the thoracic duct. He concludes that the lymphocytes may be either sent through the thoracic duct or forced directly into the circulation.

Meunier (1898) suggested that the lymphocytosis of whooping cough might have a mechanical origin, for he observed it during paroxysms of coughing. Capps (1896) and Burrows (1899) who studied patients with convulsions, and Larabee (1902) who worked with athletes running a 25-mile race, state that there is a leucocytosis

of muscular exercise in which the lymphocytes may be absolutely increased to a slight extent, but the increase in leucocytes is largely due to an increased number of polymorphonuclear cells

#### EXPERIMENTS WITH LYMPHOCYTES IN VITRO

Experiments upon lymphocytes and lymphoid tissue in vitro aid in the understanding of the reaction of lymphocytes in vivo. The simplest experiments were those of Pappenheimer (1917) who, by the use of the vital dye, trypan blue, determined the viability of the cells in various solutions. He found that hypotonic salt solutions were better borne by the lymph cells than hypertonic solutions. A pH of 6.8 to 7.2 is optimum, when solutions were made either more acid or more alkaline, the percentage of dead cells in his suspensions was greater. A temperature of 36° to 48° was optimum, above 51°C, practically all the cells were killed. Strong concentrations of oxygen or carbon dioxide increase the percentage of stained cells. Irradiation with x-ray brought about no appreciable change. When a photosensitive substance was added to a suspension of cells and the mixture exposed to sunlight for one hour, there was a great increase in dead cells. Cells from animals with chronic inanition and from old animals were more sensitive than those of younger animals. Serum or other colloid substance added to the suspension of cells, seemed to protect them.

The migration of lymphocytes has been observed in tissue cultures. Lewis and Webster (1921) found that in cultures of human lymph nodes, the lymphocytes were the first to move out from the original bit of tissue. They showed active ameboid movement. Other cells migrated, but their action was much slower. McCutcheon (1924) found that at body temperature 54 per cent of the lymphocytes in a tissue culture showed obvious locomotion during the first hour, and that by the ninth hour, 100 per cent showed locomotion. The rate increased each hour. By contrast the neutrophils had only a brief period of acceleration followed by a gradual slowing of locomotion.

Carrel and Ebling (1923) found that lymphocytes migrated and multiplied, but showed no tendency to form tissue. They did not gather into groups of cells except about foreign bodies which happened to be in the medium. The ability of the lymphocyte to utilize serum in tissue cultures has been mentioned above.

Murphy, Liu and Sturm (1922) suspended lymphocytes from thymus and from normal lymph nodes in normal serum and in serum of rats which had been exposed to x-ray. The so-called short stimulating dose was given. Counts of the cells in such suspensions were taken immediately afterward, two hours afterward and four hours afterward with the following average results

	BEGINNING OF EXPERIMENT	TWO HOURS	FOUR HOURS
Normal serum	16,500	13,000	12,000
X-ray serum	15,000	18,500	17,800

This outcome seemed to indicate that the serum from animals which had been x-rayed had a stimulating effect on lymphocytes. Microscopic examination of the cells from these suspensions showed that active mitosis was taking place whereas there was no mitosis in the cells suspended in normal serum.

In their later experiments blood was drawn from normal animals and the serum exposed to x-ray. Lymphocytes were then suspended in it and counts made as in the previous experiments. The counts from this suspension did not differ from those from a suspension in normal serum. They concluded that some change had been brought about other than that in the serum itself for stimulation of the lymphoid cells occurs only in the serum of living animals exposed to irradiation.

#### CONCLUSIONS

Studies of the lymphocytes have yielded relatively few decisive results. Of greatest clinical interest are the responses of lymphocytes to infection and to physical agents, but the real significance of such responses will be determined only when more is known about the physiology of these cells. The technique of tissue culture is improving rapidly, and study by that method may help to define the function of the lymphocyte.

The position of lymphoid tissue and of the lymph nodes and the changes which they undergo in the presence of irritants show that they have some part in protecting the body from injurious agents, but how they act is not clear. The occurrence of lymphocytosis in

association with certain infectious diseases is further evidence that lymphocytes have a part in the reaction against injurious agents, but conditions which cause polynuclear leucocytosis on the one hand, and lymphocytosis on the other are not definable

Lymphoid tissue undergoes variations with age and the changes during adolescence are especially worthy of note but the significance of these changes is not evident Physical agents which, appropriately applied, produce lymphocytosis are heat, ultra-violet rays, and roentgen rays, but investigation has not definitely revealed their mode of action

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# EXPERIMENTAL STUDY OF THE LEUCEMIAS AND LYMPHOMATA

## A REVIEW

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The literature of leucemia and aleucemic lymphoma has been reviewed to determine how the disease may be studied to the best advantage by experimental methods. It has seemed desirable to include in the survey various types of leucemia on the one hand, and on the other hand, lesions of lymph nodes such as aleucemic lymphoma, lympho-sarcoma and lympho-granuloma, for the reason that no sharp line can be drawn between them.

There has been almost unanimous agreement that none of these diseases can be transferred from one species to another. Evidence is wanting that leucemia in mammals can be transferred to other animals of the same species, and the same statement can perhaps be made of aleucemic lymphoma. In view of the widespread desire to reproduce tumors of lower animals by experimental methods, it is probable that the number of unsuccessful attempts is much larger than published records indicate. One type of tumor, which has its origin in the lymph nodes of dogs, is readily transmitted by natural and artificial means, but this so-called "infectious lympho-sarcoma" of the dog has many characters which distinguish it from the true neoplasms. The disease known as leucemia of fowls is easily transmitted to other fowls and in the opinion of most who have studied it, is caused by a filterable virus. It is noteworthy that the transmissible sarcoma of fowls described by Rous (1908) is likewise caused by a filterable virus and in this respect differs from the malignant tumors of mammals.

## EXPERIMENTS WITH HUMAN LEUCEMIA

Only one investigator has attempted to transfer leucemia from one human being to another. Schupfer (1905) injected blood from a



patient with myelogenous leucemia into the venous system of three persons with carcinoma, one died a month after the injection, the second four and one-half months, and the third ten and one-half months afterwards. Leucopenia was noted in the first case but no change was observed in the blood of the other two. A fourth patient with carcinoma received intravenously blood from a patient with acute lymphatic leucemia and a neutrophil leucocytosis present before the injection diminished slightly. This author suggests that patients with malignant growths may be unfavorable subjects for the development of leucemia.

Numerous attempts have been made to transfer human leucemia to lower animals. Especially noteworthy are experiments made on monkeys. Nette (1890) has described experiments in which four monkeys (*Macacus cynomolgus*) received into the peritoneal cavity blood (4 cc., 5 cc. or 10 grams) from a patient with myelogenous leucemia. He failed to reproduce the disease. A fifth monkey received through a laparotomy wound a piece of spleen from another patient with myelogenous leucemia, and the outcome was the same.

Blood (15 cc.) from a patient with acute lymphatic leucemia was injected by Ottenberg (1909) into a vein of a macacus monkey. A second animal received intravenously 10 cc of spleen pulp. No evidence of leucemia was discovered though both monkeys were kept under observation during six months. Hirschfeld and Jacoby (1909b) cite a similar unsuccessful experiment on a monkey.

No leucemic changes were found by Ludke (1910) in two monkeys twice injected intravenously with freshly drawn blood from a patient with myelogenous leucemia. A macacus monkey not only received leucemic blood with the same result, but also repeated injections of emulsions prepared from spleen and bone marrow of myelogenous leucemia. In two young macacus monkeys production of anemia by means of pyrodin preceded injection of blood from a patient with myelogenous leucemia. The blood was introduced into splenic tissue and into the peritoneal cavity, but leucocytosis was the only change which followed.

In experiments cited by G. Muller (1913) chronic myelogenous leucemia was not reproduced in monkeys by injection of from 5 to 10 cc of blood into subcutaneous tissue, veins, peritoneal cavity, substance of the spleen or bone marrow.

Unsuccessful experiments on 33 monkeys (*Macacus cynomolgus*) were made by Leschly and Thomsen (1917) Blood (3 to 5 cc) from patients with lymphatic or myelogenous leucemia was injected, in most instances into the veins but occasionally into subcutaneous tissue or into the peritoneal cavity Experiments with lymph node and spleen from a patient with pseudo-leucemia were fruitless

Unsuccessful attempts to transfer leucemia to dogs and rabbits are described by Mosler (1872) Netti (1890) injected blood of splenomyelogenous leucemia into the ear vein and peritoneal cavity of 4 rabbits and into the subcutaneous tissue of mice Intravenous injection of leucemic blood into 3 pigs, in one instance preceded by withdrawal of blood, was equally unsuccessful, as was also introduction into a pig of a bit of spleen of myelogenous leucemia Inoculation of fowls was likewise without result Teichmüller (1899) cites unsuccessful experiments on guinea pigs and mice and Angebaud (1908) on guinea pigs

The only investigator who has claimed success in transferring leucemia of man to lower animals is Wiczowsky (1913) A hen which received pleural exudate from a patient with leucemia exhibited 6 weeks later blood changes similar to those of the patient but different, it is said, from those of leucemia in fowls Post-mortem changes showed the presence of a disease resembling leucemia It is, however, not improbable that the fowl suffered from spontaneous leucemia, for experiments made by other investigators, namely, Netti (1890) Hirschfeld and Jacoby (1909a), and Ellermann (1921b) had no significant result

After the injection of leucemic blood into rabbits Schupfer (1905) found leucocytosis but none of the changes of leucemia Inoculation of bats was unsuccessful

#### LEUCEMIA IN MAMMALIAN SPECIES

Veterinary literature contains many references to leucemia in domestic animals but few descriptions of changes in the blood and lesions of blood forming organs in sufficient detail to identify the disease with certainty In many instances diagnosis of leucemia has been made when changes in the blood have had little resemblance

to those in leucemia in man. In other instances no examination of the blood has been made during life and specimens prepared from the heart's blood after death or contents of blood vessels observed in histological preparations have supported uncertain deductions concerning the nature of the disease. Special attention will be given to cases in which the blood and blood-forming organs have been adequately studied. Although reports of lymphatic leucemia in animals often describe doubtful changes in the blood and establish only the occurrence of lymphomatous tumors widely distributed in lymph nodes and other organs of the body, yet numerous instances of similar lymphomata and lymphomatous infiltration do occur with no leucemic change in the blood. Special attention will be given to leucemia in dog, cattle and mice, because there is a considerable accumulation of information about the disease in these animals.

Changes which might be mistaken for leucemia have been produced experimentally. Transient leucemia-like changes in the blood of a macacus monkey were produced by Ludke (1910) by subcutaneous injection of pyrodin (0.05 gram) followed, after two weeks, by four injections of virulent streptococci made during the course of one and a half weeks. Before the injection of pyrodin, the leucocytes numbered 8800 and the differential count was normal, before the injection of streptococci there was moderate anemia, the leucocytes numbered 21,400 but the differential count had undergone no great change. After each injection of streptococci, the eosinophil cells rose to approximately 24 per cent. Two weeks after the last injection of streptococci, the leucocytes amounted to 67,000 and the differential count was as follows: lymphocytes 27 per cent, polymorphonuclear leucocytes 21 per cent, eosinophils 8 per cent, large mononuclear and transitional forms 18 per cent, nucleated red corpuscles 16 per cent, neutrophil myelocytes 9 per cent, eosinophil myelocytes 10 per cent. Similar changes were found after four weeks, but after three months the blood was normal.

Almost identical changes were produced in four dogs by similar procedures. Ludke (1910) injected pyrodin (0.1 gram) subcutaneously into a dog whose blood was approximately normal (leucocytes 13,000), and after intervals of six, eleven and fourteen days injected intravenously small quantities of both streptococci and staphylococci.

Ten days after the last injection the leucocytes were almost 90,000, there was anemia and the differential count of the leucocytes was as follows lymphocytes 22 per cent, polynuclear leucocytes 54 per cent, eosinophils 6 per cent, mononuclear and transitional forms 8 per cent, myelocytes 10 per cent. The animal died ten days later. Similar changes were found in the blood of three dogs which received the same treatment. In two of them, which survived, leukemia-like changes in the blood disappeared.

*Leucemia and related diseases in the dog* In records of leukemia from the older literature of the subject there are no counts of red or white blood corpuscles and no differential counts. In the case described by Siedamgrotzky (1872) the spleen was enormous (1175 grams), all of the lymph nodes were enlarged and the relation of white to red blood corpuscles was 1 to 15. Bollinger (1874) found in a dog hyperplasia of the spleen and lymph nodes and leucemic infiltration of the lungs and liver. The ratio of white to red corpuscles in the heart and coronary artery after death was 1 to 5. He designated the condition splenic and lymphatic leukemia. An emulsion prepared from the spleen was injected through the chest wall into the lung of a normal dog without noteworthy changes. In a second dog there was a lymphoma the size of a child's head arising from the spleen which was otherwise normal in appearance, the relation of white to red corpuscles in the blood of the coronary artery was slightly increased (1 to 30 or 40) and also in the splenic vein (1 to 10 or 15). The condition was called simple splenic leukemia because, in association with other evidence of leukemia, the spleen was the site of a tumor mass.

Leucemia in a cat was also described by Siedamgrotzky. The animal died with internal hemorrhage, there was hyperplasia of lymph nodes and the spleen was double the usual size. He designated the condition splenic lymphatic leukemia of slight grade.

Instances of leukemia in which blood and blood-forming organs were carefully studied are described by Lmule-Weil and Clerc (1904, a, b, c, 1905, a, b, c). In one animal the white blood corpuscles numbered 320,000 ten days before death, the lymphocytes being 88 per cent, monocytes 3 per cent, plasma cells 1 per cent and polynuclear leucocytes 8 per cent. All lymph nodes, the liver and spleen were enlarged. The bone marrow was almost wholly replaced by

lymphocytes In the lymph nodes, liver, kidneys and mammary gland normal structure of the organ was obliterated in places by infiltration with lymphocytes In a second animal the leucocytes, one month before death, numbered 18,700, polynuclear leucocytes being 59.8 per cent and lymphocytes 28.4 per cent Immediately before death the leucocytes were 21,200, polynuclear leucocytes 24 per cent and lymphocytes 60.5 per cent The lymph nodes were enlarged There was no autopsy

The opinion of Émile-Weil and Clerc (1904b) that their first case is a typical instance of lymphatic leucemia is confirmed by their description The high white blood count, the predominance of lymphocytes, the general enlargement of lymphatic nodes and the lymphomatous infiltration of bone marrow, spleen, liver and kidney identify the disease Unsuccessful attempts were made by these observers to transfer lymphatic leucemia by inoculation with blood and with lymph nodes of this animal Intravenous (15 cc.) and intraperitoneal (50 cc) inoculation with blood and subcutaneous inoculation with tissue from an enlarged lymph node failed to reproduce the disease In their second case the character of the disease is wholly undefined

The two following instances described by Wirth (1920) were perhaps examples of aleucemic lymphoma rather than of leucemia In a dog with general enlargement of lymph nodes the leucocytes were 24,000, polynuclear leucocytes 60.1 per cent and lymphocytes 39.1 per cent At autopsy the lymph nodes and tonsils were found to be enlarged There was catarrhal bronchitis and hemorrhagic gastroenteritis The spleen was much enlarged and the liver contained numerous large foci in which cells of lymphoid type were massed together The structure of the spleen and of the lymph nodes was obscured by the same kind of cells In a second animal the leucocytes were estimated at approximately double the normal number, the lymphocytes were 43.2 per cent, two thirds being large lymphocytes The lymph nodes were much swollen and the liver and spleen were enlarged by leucemic infiltration

A disease regarded as myelogenous leucemia was seen in two dogs by Émile-Weil and Clerc (1905, b, c). In one instance the leucocytes numbered 165,000 of which 93 per cent were polynuclear leucocytes

and 7 per cent mononuclear leucocytes, there were no myelocytes. The lymph nodes were enlarged but there was only a slight swelling of the spleen. The bone marrow was said to contain myeloblasts almost exclusively. In the second case white blood corpuscles were roughly estimated at 50,000 and the differential count gave polynuclear leucocytes, 88 per cent, eosinophil cells, 0.4 per cent, monocytes, 5.6 per cent, myeloblasts (cells of Turk), 4 per cent, and myelocytes, 2 per cent. In the bone marrow these were chiefly myeloblasts. Infiltration of the organs with cells regarded by the authors as myeloblasts was thought to be leucemic. Changes in the blood of these two animals do not establish the diagnosis of leucemia.

Wirth (1920) has described eleven instances of myelogenous leucemia in dogs but says that the typical blood changes of myelogenous leucemia as they occur in man have not been observed in domestic animals. Anemia, in these cases, was occasionally advanced. A moderate increase of leucocytes usually occurred (25,000 to 40,000), exceeding 45,000 in only one instance (87,000). This increase in white corpuscles was in great part referable to polymorphonuclear leucocytes (usually 85 or 95 per cent). Eosinophil cells were diminished and myelocytes were present in small number, namely, 0.1 to 3 per cent (in one instance 6 per cent) and a few cells regarded as myeloblasts were found (0 to 4 per cent). These changes, the author states, differ widely from those in human leucemia and resemble advanced leucocytosis, so that the disease in terms of human pathology might be regarded as "myelogenous aleucemia" or "subleucemia."

In all of these animals the general enlargement of the lymphatic nodes was greatest in the submaxillary and cervical nodes. The spleen was greatly enlarged in 8 instances and in one not apparently enlarged. In two instances it contained "leucemic" nodules. The liver was usually enlarged and contained gray-white nodules. In most instances there was recognizable hyperplasia of the bone marrow. Histological examination of tissues was made in 7 cases and disclosed, the author asserts, typical leucemic infiltration of internal organs. The bone marrow was hyperplastic and contained granular cells in various stages of development, erythroblasts, and giant cells, and exhibited, the author believes, the characters of a pure myeloid hyperplasia. In six instances the liver, spleen, kidneys, lungs or

lymph nodes contained accumulations of cells which in great part consisted of polymorphonuclear leucocytes. Myelocytes do not appear to have been found. Giant cells resembling those of the bone marrow were seen and about them were cells which even in the absence of special stains for specific granules exhibited the characters of myeloid cells. Histological examination of the bone marrow and accumulation of myeloid cells in other organs furnished the chief evidence, in the opinion of Wirth, that this disease of dogs has the characters of myelogenous leucemia.

The occurrence in a dog of myelogenous leucemia identified by changes in the blood and in the organs is cited by Ludke (1910). Emulsions prepared from fresh bone marrow and spleen of this animal were repeatedly injected into the venous systems of six young dogs. After an interval of six weeks one of them had a leucocytosis of 85,000, anemia with nucleated red blood cells and myelocytes varying from 5 to 10 per cent. These leucemia-like changes disappeared after about three weeks.

Tumors described as lympho-sarcoma and formed by small lymphoid cells have been repeatedly seen in dogs. Frohner (1894) described lympho-sarcoma of the heart and kidney. Loubet and Babeau (1897) found a voluminous mass at the base of the heart which perhaps had its origin in the thymus with metastases in peritoneum, liver, kidneys and scrotum. Magnusson (1916) observed a lympho-sarcoma of the heart which apparently had its origin in the lymph nodes of the neck, another of the kidney or adjacent lymph nodes with metastasis to the heart, and a third infiltrating the myocardium. "Pseudo-leucemia" in a dog was described by Milks and Goldberg (1919). The animal died after an illness of two months, the leucocytes were not increased. Mesenteric lymph nodes formed an immense mass and other lymph nodes were so greatly enlarged that their total weight was approximately one twelfth of the body weight. Accumulation of lymphocytes obliterated the normal structure. The spleen was greatly enlarged, contained conspicuous white nodules and was infiltrated with cells resembling lymphocytes. In the liver there was massive periportal infiltration with lymphocytes.

The foregoing review shows that lymphatic leucemia occasionally occurs in dogs and that lymphomatous tumors are not uncommon.

The nature of the disease described as myelogenous leucemia in dogs is as yet uncertain

*Leucemia and related diseases in cattle* Little information can be obtained from instances of leucemia in cattle in the older literature of the subject (Wolff, 1892, Baranski, 1894) Examination of the blood after death is insufficient to establish the diagnosis unless careful study of the contents of the blood vessels in various organs is made by means of microscopic sections

The description by de Jong (1903) of pure splenic leucemia in a calf five weeks old is worthy of little consideration, for the blood examination (white blood corpuscles 30,000) was made from the blood of the heart after death at a time when all of the organs had undergone post-mortem decomposition The bone marrow and lymph nodes, the author says, showed no changes suggesting leucemia except that the spleen was immensely enlarged

In a cow Ramazzotti (1907) found leucemia "lymphadenic" The spleen was swollen and consisted almost wholly of enlarged follicles In the lymph nodes lymphocytes in great number obliterated the distinction between cortex and medulla In the liver there were gray-white flecks consisting of lymphocytes crowded together, and the blood vessels were filled with cells among which lymphocytes were numerous

Leucemia, regarded as lymphatic in type, in a cow (five years old), is adequately described by Aubertin and Morel (1913) There was a general hyperplasia of lymph nodes, those of the periscapular region measuring as much as 20 cm in length There was the homogeneous appearance seen in association with human lymphatic leucemia The spleen was enlarged and infiltrated with lymphocytes but the organ presented no remarkable change The white corpuscles were not counted but 20 were found in each field of the oil immersion lens, and the differential count was as follows polymorphonuclears, 3 per cent, eosinophils, 1.5 per cent, mononuclears, 3 per cent, large mononuclears, 1 per cent, lymphocytes, 84.5 per cent and large lymphocytes, 6 per cent "Large lymphocytes" are cells occasionally found in normal blood of the cow They have basophil cytoplasm resembling lymphocytes but exceed polynuclear leucocytes in size No myelocytes, myeloblasts or nucleated red corpuscles were observed



In a second animal, a calf two months old, there was hypertrophy of all lymph nodes, the lumbar and mesenteric nodes being enormous. The spleen was not enlarged but there was advanced leucemic infiltration of the liver and kidneys. No examination of the blood was made during life but the blood vessels, in sections prepared for microscopic examination, contained a great number of white corpuscles most of which were lymphocytes.

Leucemia is said to be endemic among cows in certain districts of East Prussia. The disease as described by Knuth and Volkman (1916) is associated with hyperplasia of lymphoid tissue often with tumor formation in heart-muscle, kidneys, mucosa of stomach and intestine but with none in liver, spleen and bone marrow. Lymphocytoma of the orbit has been seen. There is an increase of white blood corpuscles with predominance of large cells resembling lymphocytes. The disease has been designated "lymphocytomatosis."

In lymphocytomatosis of cattle du Toit (1917) found that cells of lymphoid type are greatly increased. The cell, designated lymphoidocyte, which is predominant in the blood, varies much in size, has a round, indented, or bilobed nucleus, and is the undifferentiated precursor of the lymphocyte. It is perhaps the undifferentiated forerunner of all the white blood cells as well, for it cannot be distinguished from cells which form granulocytes. The disease often resembles, du Toit believes, acute lymphatic leucemia of man. Nevertheless, in some instances the blood contains small lymphocytes in large number and has the characters of chronic leucemia of man. Since transitions occur between the two forms it is improbable that they represent two distinct diseases. In normal full-grown animals the percentage of lymphocytes is much higher than in man, namely 49 per cent, while in calves the lymphocytes may number 80 per cent or even more. With lymphocytomatosis in fully grown cattle the lymphocytes may reach 96 per cent, neutrophil cells may fall to 2 per cent and eosinophil cells may completely disappear from the blood.

It has not been found possible to transfer the disease from a sick to a healthy animal. In animals which Knuth and Volkmann injected with blood, milk, urine and emulsion prepared from the lymph nodes and kidneys of animals with lymphocytomatosis, du Toit found a

polynuclear leucocytosis but no blood changes like those of the original disease

Lympho-sarcoma is evidently not unusual in cattle for Magnusson (1916) collected from the literature of the subject 21 instances and described 5 of his own, in all of which the lesion implicated the heart. In some cases the tumor had its origin in the lymph nodes at the base of the heart and in others the primary tumor was in the abdomen. Widespread metastasis was not uncommon.

*Leucemia and related diseases in mice* Diseases characterized by hyperplasia of lymphoid tissue are as varied in mice as in man. Lymphomata having their origin in the lymph nodes are not associated with tumor-like lymphoid infiltration of the internal organs. In some instances these lesions are accompanied by changes in the blood resembling those of lymphatic leucemia and in some there is no recognizable lymphocytosis. Furthermore, lymphomata having the characters of sarcomata are recognizable but they do not form a well-defined group. It is possible that all such lesions are varied manifestations of the same process.

Numerous unsuccessful efforts (Tyzzer, 1907, Haaland, 1911) have been made to transfer leucemic and aleucemic lymphomata from one mouse to another.

Haaland has noted the leucemia of mice in mother and daughter. The occurrence of several instances of lymphomata (Haaland) or of leucemia (Fajersztajn and Kuczynski, 1892) in the same cage of mice is perhaps explained by hereditary transmission.

Lymphomata in mice with carcinoma or adenoma have been seen by Hurland and by Simonds, and lymphomata have been found by several observers in strains of mice in which carcinoma were numerous.

A disease in mice with some resemblance to Hodgkin's disease has been described by Jobling (1910) by Simonds (1925), and perhaps by Tyzzer (1909).

Myelogenous leucemia occurs in mice and is accompanied by infiltration of the organs with cells resembling bone-marrow cells (Tyzzer, 1909, Simonds, 1925).

A sharply circumscribed tumor mass composed of large lymphoid cells was found by Tyzzer (1907) in the inguinal region of a white mouse. Inoculation of this tumor, designated lympho-sarcoma, into

seventeen mice was unsuccessful. A second tumor of similar character formed a large mass in the mediastinum and was accompanied by smaller nodules in the pericardium and lungs.

In a second publication Tyzzer (1909) has described 10 lymphoid tumors. Masses with the appearance of primary growths occurred in the inguinal region, thymus or mesentery, but in three instances the site or origin was not evident because the tumor had been disseminated throughout the mesenteric lymph nodes and other organs. With most of these tumors there was widespread lymphoid infiltration of the spleen, liver, kidney, pancreas, etc. In one tumor there was great variation in the size of cells, the smallest being equal to lymphocytes, the largest being multinucleated and as large as bone-marrow giant cells. In one instance, regarded as lymphatic leucemia, sections of the organs showed that the blood vessels contained in large number lymphoid cells identical with those of the tumor, the mesenteric lymph nodes were enlarged and there was lymphoid infiltration of the liver. Three tumors which Tyzzer does not classify had characters which according to Simonds (1925) suggest myelogenous leucemia, myelocytes having been present in the blood.

Pseudo-leucemia (aleucemic lymphoma) was seen in five mice by Haaland (1905). The animal first affected was placed in a cage with other mice, four of which developed the same disease, whereas mice in other cages did not. Numerous particles of the tumors were unsuccessfully inoculated into other mice.

Later Haaland (1911) found in female mice 21 tumors consisting of lymphoid tissue. From each of two more or less localized lymphomata approximately 40 inoculations were made with negative result. Over 100 mice were inoculated from widely distributed lymphomata in another mouse but no new growths were formed. In an instance of lymphatic leucemia with a blood count of 109,500 Haaland made transplants from spleen, thymus and lymph nodes intravenously and intraperitoneally into more than 100 mice but failed to reproduce the disease. Leucemia occurred in a second mouse, the daughter of that from which the last-mentioned transplants were made, and the maximum blood count was 655,000. Lymphoid tumors from this animal were inoculated into 112 mice with entirely negative result.

Lymphomata with characters of pseudo-leucemia, (aleucemic

lymphoma) and of lympho-sarcomata occur in mice even more frequently than leucemia. Lymphomata in 15,000 autopsies performed on white mice which were used by Maud Slye in the study of the heredity of tumors were carefully studied by Simonds (1925). Among 316 animals with conspicuous enlargement of the lymph nodes he found 67 with leucemia, 111 with pseudo-leucemia, 51 with lympho-sarcoma, and 4 with a condition resembling Hodgkin's disease (lymphogranulomatosis). Each one of these diseases is described by Simonds.

Leucemia in mice is characterized by readily definable changes:

- (a) There is a great increase in the number of white cells as is shown by examination of the contents of blood vessels in sections of various tissues prepared for microscopic examination.
- (b) There is enlargement of the spleen and of widely separated groups of lymph nodes. The normal histologic architecture of these organs is obliterated by excess of white cells and there is invasion of the capsule of the lymph nodes.
- (c) Leucemic infiltration of various organs occurs and is especially conspicuous in liver, lungs and kidneys, often with enlargement. In lymphatic leucemia the lymphocytes of the blood, which are relatively and absolutely increased in number, are in most instances larger than normal lymphocytes. Leucemic infiltrations of organs, for the most part perivascular, are usually composed of cells similar to those predominant in the blood.

In myelogenous leucemia there has been observed an enormous increase of nucleated cells of the blood, in great part young polymorphonuclear leucocytes with ring-shaped nuclei, myelocytes are numerous. Similar cells have been found in lymph nodes, spleen and other organs. Megakaryocytes have been present but in no greater number than in lymphatic leucemia. The spleen has been somewhat larger in myelogenous (the average being 15 times the normal) than in lymphatic leucemia (12 times the normal) but there has not been the great difference found in the two types in human beings.

In five mice there were lesions which had the characters of Sternberg's leuco-sarcoma and were intermediate in character between lympho-sarcoma and leucemia. As in lympho-sarcoma there was a tumor mass arising in the mesenteric lymph nodes, thymus or other

organs and invading the surrounding structures. The white cells of the blood within the vessels of all the organs were notably increased.

Pseudo-leucemia in mice resembles leukemia in its gross and microscopic characters but is not accompanied by an increase of the white cells of the blood. The cells which are predominant in the enlarged lymph nodes and spleen and form perivascular infiltrations of the lungs, liver, kidneys and other organs have usually been somewhat larger than lymphocytes. The spleen is enlarged to the size seen in lymphatic leukemia and cells resembling megakaryocytes are found in about the same number as in this disease. On the one hand, there are apparently transitions between pseudo-leucemia and leukemia with an increase of lymphocytes in the blood insufficient to establish the diagnosis of leukemia. On the other hand, there are transitions between pseudo-leucemia and lympho-sarcoma in which the tumor-like growth in at least one set of nodes is actively invasive.

Lesions designated lympho-sarcoma have begun in one lymph node or at least in one group of lymph nodes and have invaded adjacent structures. The primary tumor was intrathoracic in 32 mice, intra-abdominal in 8, subcutaneous in 9 and "too generalized to determine the original site" in 2. The spleen has not usually been enlarged but in a few of these animals it contained sharply differentiated masses of proliferating cells similar to those of the primary tumor. Mitotic figures are numerous but apparently not more numerous than in leukemia and pseudo-leucemia. When organs such as the lung, liver and kidney have been infiltrated with lymphoid cells, the infiltration is in apparent continuity with the primary growth, but in most instances these organs have not been implicated. The uncertainty of diagnosis of lympho-sarcoma is indicated by the number of instances in which there has been a difference of opinion among those concerned with the study of these tissues. Of 51 instances included in the group of lympho-sarcoma, in 16 the character of the lesion was doubtful.

Simonds (1925) has discussed at length the relation of leucemic and aleucemic lymphoma to lymphoid hyperplasia in mice. Hyperplasia follows acute and chronic infections but conspicuous hyperplasia unassociated with evident infection is even more common. The criteria by which this hyperplasia is separated from leucemic and aleucemic lymphoma are not wholly satisfactory and it is not im-

probable that some instances of apparently simple hyperplasia belong to the lymphomata. With lymphoid hyperplasia, Simonds says, the lymph nodes do not reach the massive size seen in leucemia and pseudo-leucemia. There is slight if any invasion of the capsule and surrounding tissues, lymphocytes are more nearly normal in size and appearance, periportal infiltrations are less extensive and infiltration of hepatic sinusoids is absent though there may be some accumulation of lymphocytes within the sinusoids. Perivascular infiltration of lungs and kidneys is infrequent and moderate in lymphoid hyperplasia, whereas in leucemia and pseudo-leucemia there is advanced and fairly uniform infiltration of these organs.

Lesions regarded as closely related to lymphogranulomatosis (Hodgkin's disease) were found in 4 mice from the 15,000 autopsies and are described by Simonds, the disease affected in one instance the retroperitoneal lymph nodes, in a second the cervical and inguinal nodes, in a third the inguinal and mesenteric, and in the fourth the mesenteric nodes alone. The normal lymphoid structure was obliterated by irregularly disposed accumulations of large cells, some of which resembled fibroblasts, and some had round, indented or multiple nuclei. The spleen was enlarged in one instance to 16 times the normal size and showed histological changes similar to those in the lymph nodes. In 3 of these mice there was periportal infiltration with lymphocytes and large cells resembling those in the lymph nodes and spleen. In the first animal cited a mass at the hilum of the kidney had the same structure as the altered retroperitoneal lymph nodes.

*Leucemia and related diseases in other mammalian species.* A disease regarded as similar to chronic lymphatic leucemia was observed by Massaglia (1923) in a monkey (*Cynocephalus sphinx*). The lymph nodes, especially the inguinal nodes, were much enlarged and the spleen was palpable. The count of white corpuscles was only 36,000, 65 per cent of which were lymphocytes and 17 per cent large mononuclear or transitional forms. Since no autopsy is described the diagnosis remains doubtful.

Cases of leucemia in the horse are cited by Bollinger (1874), Nocard (1880, 1882) and others, but I have found no instances in which the nature of the disease has been established.

Lympho-sarcoma of the horse, at times generalized and similar to that which occurs in cattle, is evidently not uncommon for Magnusson (1916) has collected 3 instances from the literature of the subject and has added two of his own, in all of which the heart was implicated

Leucemia in the pig is described by Leisering (1865) who found changes in the spleen, liver, lymph nodes and blood. More detailed information concerning this case, regarded by Bollinger as splenic and lymphatic leucemia, is wanting. Furstenberg (1870) found what he called splenic-lymphatic and myelogenous leucemia, there was enlargement of lymph nodes, spleen and liver, hyperplasia of bone marrow and an enormous increase of white blood corpuscles, the ratio to red corpuscles being as 1 to 2. Bollinger described an instance of splenic leucemia in the pig, there was enlargement and leucemic infiltration of spleen and kidney and infiltration of the liver and lungs. The ratio of white to red corpuscles after death was as 1 to 5. Available information concerning leucemia in the pig is unsatisfactory.

Two instances of "lymphomatosis" in pigs described by Morlot and Vitu (1923) were found among 40,000 pigs slaughtered during one year. Inguinal, crural, lumbar renal and hepatic lymph nodes were much enlarged and tumor-like nodules, formed by lymphocytes somewhat larger than the usual, occurred in liver and kidney.

Fox (1923) found in an opossum a massive lymphoma composed of larger lymphocytes, there was widespread infiltration at the margin of the tumor and there were similar cells in distant organs. The blood examined in sections of the organs, contained nucleated cells in excess. A tentative diagnosis of lymphatic leucemia was made.

Leucemia in rabbits has apparently not been seen. Lympho-sarcoma is described by Dessy and Aberastury (1903) and by Wallner (1921).

In guinea pigs Miguez (1918) studied a tumor of the neck with the characters of lympho-sarcoma, there was lymphoid infiltration of the liver and kidneys. By subcutaneous inoculation the tumor was transferred to other guinea pigs through nine generations.

*Conclusions* The foregoing survey shows that much of the literature concerning leucemia and related diseases in mammals is untrustworthy. Nevertheless, it is evident that leucemias conforming with the types found in man occur in many, if not in all, domestic animals,

and in small animals available for experimental studies Aleucemic lymphomatosis apparently occurs much more frequently Opportunity for the experimental study of leucemias resembling those of man is not lacking, but experiments have been as yet unfruitful

#### INFECTIOUS "LYMPHO-SARCOMA" OF DOGS

The disease usually designated infectious lympho-sarcoma of dogs is anomalous both as an infection and as a tumor though it has the characters of both It is transmitted as a venereal disease and begins in the male as a nodular infiltration of the corona of the penis or in the female as nodular and papillary growth of the vaginal mucosa Catarrhal inflammation usually precedes the appearance of the tumor, but may be absent Tumor-like nodules are formed, in some instances, in the cutaneous, pelvic and abdominal lymph nodes Isolated growths may occur in the skin of the groin, abdomen, back, neck and legs and occasionally in the internal organs These growths are usually circumscribed and encapsulated and free from evidence of inflammation, but with longstanding disease there may be diffuse infiltration of the skin or mucous membrane with superficial ulceration Spontaneous regression with atrophy and fibrosis of the tumor may occur The tumors are grayish white and yield a mucinlike fluid on pressure The cells composing them are large, round or polygonal with a single nucleus, and occur in cords supported by thin strands of fibrous tissue Mitotic figures are often seen

The disease has been described in countries far apart, namely in Russia, United States, France, Germany and England Sticker, Woglom (1913) says, obtained specimens of the tumors studied by several widely separated observers and submitted them to a number of German pathologists All regarded the tumor as a round-cell sarcoma, the usual histological changes of inflammation being absent According to Beebe and Ewing (1906) the tumor resembles a large-cell lympho-sarcoma but appears to be much less malignant than the corresponding tumor of man The type of cell which gives rise to it is uncertain

Nowinsky (1876) has described the transfer of a tumor designated Carcinoma medullare naris from one dog to a second dog by implantation and again from the latter to a third animal It is possible



that the growth was identical with the transmissible lympho-sarcoma of dogs, for Wehr (1888) has described as carcinoma of the vagina and Geissler (1895) as carcinoma of the prepuce, tumors which they succeeded in transferring by implantation into other dogs Sticker (1904) later had the opportunity of examining both the spontaneous tumor and the transplanted tumors of Geissler and found that they had the same structure as the transmissible lympho-sarcomata which he had studied

Smith and Washbourn (1897) observed the occurrence of the disease in 11 of 12 females served by a dog suffering from a growth upon the penis Three of them were subsequently served by a second dog which later developed a growth upon the penis Retrogression of the tumor did not occur in any of the animals described by Smith and Washbourn Growth was slow at first but later more rapid and after a year or eighteen months the vagina was filled by a mass as large as an orange No autopsies were made upon animals which died as the result of the disease

After subcutaneous implantation Sticker (1904, 1906) observed the appearance of a nodule within from two to six weeks The rapidity of growth varied much, after several months the mass often attained the size of a hen's egg After intraperitoneal inoculation a single growth attached to the omentum appeared or multiple disseminated nodules occurred In some instances secondary tumors were formed in the regional lymph nodes and occasionally multiple nodules were seen in the lungs, liver, spleen and elsewhere Attempts to reproduce the tumor by intravenous injection were unsuccessful

In 45 subcutaneous implantations there was progressive increase in the size of the tumor, but in 18 instances, after a period of growth lasting from thirty-one to one hundred seven days, the tumor diminished and with a few exceptions disappeared completely In one instance a tumor which had increased to the size of a hen's egg during one hundred seven days disappeared within fourteen days With intraperitoneal implantation, regression occasionally occurred but was less frequent than after subcutaneous injection

Duplay and Cazin (1894) inoculated infectious lympho-sarcoma of dog by bringing tumor material into contact with the scarified prepuce Smith and Washbourn (1898a) by similar procedure inoculated the vagina

Sticker (1906) transferred the disease to two foxes out of three inoculated, but failed in the inoculation of cats, guinea pigs, rabbits, rats and mice

Intact cells are apparently essential to successful transmission, for Sticker found that extracts are harmless after complete comminution of the cells by rubbing in a mortar with sand or after filtration through paper or earthenware Centrifugalization removed from a suspension material capable of reproducing the tumor Exposure to cold at  $-11^{\circ}\text{C}$  for twenty-four hours failed to destroy transmissible material, but in experiments in which tumor was preserved at  $-11^{\circ}\text{C}$  for long periods, new growth failed to occur as the result of implantation Exposure to a temperature of  $50^{\circ}\text{C}$  for two hours did not destroy viability It is noteworthy that a tumor was produced by cells preserved in glycerine with the addition of some normal salt solution for one hundred thirteen days It is questionable whether cells remain alive under such conditions

Attempts to find microorganisms associated with the tumor have failed Extracts of tumor tissue passed through a Berkefeld filter are no longer infectious

The transmissible new growth of dogs, according to Bashford, Murray and Cramer (1905) does not have the characters of a true neoplasm They observed that with natural infection connective-tissue cells adjacent to the tumor increased in size and underwent changes which converted them into tumor cells Nevertheless the increase in size of the tumor mass was mainly due to division of cells which had the distinctive characters of the tumor cells When tumor grafts were introduced a new tumor was formed by the transformation of connective-tissue cells of the host into cells indistinguishable from those of the tumor The authors regard the tumor as connective-tissue reaction caused by an unknown virus

Wade (1907) who came to the same conclusion, found that the tumor following inoculation was formed in part by implanted cells and in part by transformed cells of the host Lymphocytes of the blood increased with increase in size of the tumor Wade designated the tumor infective sarcoma and believed it to be in the borderland between infectious granuloma and true neoplasm

Investigations were undertaken by Beebe and Ewing (1906) to

determine whether the new growth is formed by proliferation of the transplanted cells or by stimulation of the surrounding tissue cells. It was assumed that a neoplasm will develop by multiplication of engrafted cells whereas in an infectious disease cells which have been introduced into the tissues will undergo necrosis while the surrounding cells of the host will proliferate under the influence of the infecting virus. They introduced small pieces of tumor into the subcutaneous tissue of dogs and removed them at intervals of from one to twenty-one days after inoculation. The central part of the tumor had undergone necrosis, but some cells had persisted and multiplied by mitosis. Areas in which fibroblasts and tumor cells were mingled, were interpreted by Bashford, Murray and Cramer (1905) as evidence of the formation of tumor cells from fibroblasts, but Beebe and Ewing maintained that the implanted tumor cells could be recognized throughout the early stages of growth and readily distinguished from the fibroblasts of the host.

The observations of Beebe and Ewing upon the fate of transplants have been confirmed by Hunter, Laws and Loeb (1910). Cells at the periphery of the transplanted mass survive, undergo mitotic division and form the new tumor. At the end of the first week infiltration of tumor cells into the surrounding tissue of the host begins. The cells of the host do not take part in the formation of the growth.

Animals in which infectious lympho-sarcoma has undergone retrogression cannot be reinoculated with the tumor. Sticker (1906) describes 13 unsuccessful attempts to reinoculate dogs from one to one hundred six days after the beginning of retrogression. In one experiment inoculation failed eight days before retrogression began, but in another experiment, in which inoculation was made eighteen days before the beginning of retrogression, transplantation succeeded. The author reaches the conclusion that there is a general immunity which hinders the growth of the sarcoma cells. Smith and Washbourn (1898b) have described four experiments in which inoculation was unsuccessful after retrogression of the tumor.

Injection of blood serum from dogs in which lympho-sarcoma had undergone retrogression into dogs with implanted tumors was followed by diminution of the tumor in two experiments of Sticker (1906). Crile and Beebe (1908) implanted the transmissible growth into dogs

After recognizable tumors had made their appearance the animals were transfused from one to four times with blood in considerable quantity (425 to 1500 cc) derived from animals which were naturally immune or had spontaneously recovered from the tumor. Of the 10 animals treated by transfusion, 7 were completely cured, in 2 there was some retrogression of the tumor, and 1 died with no evidence of retrogression. The authors conclude that although the immunity is not analogous to bacterial immunity, passive immunity may be produced by transfusion of blood from resistant animals.

After establishment of tumor growth, reinoculation was at first no longer possible according to Sticker (1907a). As the tumor increased in size there came a time when inoculation in any part of the body was again successful. Sticker believed that in the first phase no metastasis was possible, whereas in the second metastases were readily formed. He defined a premetastatic and a metastatic stage.

Bergell and Sticker (1907) observed the disappearance of these tumors after the injection of hepatic enzymes into them. Beebe and Tracy (1907) thought that certain bacterial toxins destroyed the tumor. Temporary retrogression of lympho-sarcoma of dogs following subcutaneous administration of atoxyl is described by Sticker (1908). He claims to have obtained the same result when he injected blood and organ extracts of other species into the tumor itself and to have caused complete disappearance of the tumor in two instances by the combined injection of atoxyl and foreign protein.

*Conclusions* The transmissible tumor of dogs has histological characters which are similar to those of lympho-sarcoma but the origin of the cells which form the tumor is uncertain, and it has not been shown that they are lymphocytes or are derived from lymphocytes. Such growths have little resemblance to tissue newly formed as the result of inflammation. Their transmission from one animal to another is like transmission of a contagious disease, but no micro-organism has been found in constant association with them. Resistance which appears in animals with the tumor has some resemblance to that caused by bacterial infection. Many experiments furnish evidence that transmission from one animal to another is successful only when intact tumor cells are transferred to the new host, but the growth has been reproduced with material preserved in glycerine.

One group of observers maintain that transplanted tumor cells undergo necrosis, and that the new tumor is derived from cells of the host. Another group hold the opinion that the tumor is formed by multiplication of transplanted tumor cells. The nature of the so-called infectious lympho-sarcoma of dogs is as yet undetermined.

#### LEUCEMIA OF FOWLS

Diseases with close resemblance to those affecting the blood-forming tissues of man are frequently observed in fowls. Unlike the leucemias of man they may be transmitted by inoculation from one bird to another of the same species. Furthermore, like the well-known sarcoma of fowls (Rous, 1908) the leucemia of fowls is, it is asserted, transmissible by a filterable virus and in this respect differs from similar disease of mammals.

Lymphomata appearing in the liver of fowls and composed of cells which resembled the large lymphocytes of the blood were first described by Butterfield (1905). In the same paper he cited five instances of lymphomata with leucemia seen by Mohler. In the latter, new formation of lymphoid tissue had occurred in the liver and spleen and occasionally in the lungs, intestine, kidney or heart. In the blood vessels examined in sections of the organs, cells resembling lymphocytes were present in abnormal number.

Warthin (1907) has studied a similar condition during life and after death and finding a conspicuous increase of large lymphocytes in the blood has designated the disease "lymphatic leucemia of the large-cell type". He has described two instances of aleucemic lymphomata of fowls. Leucemia of fowls has been described by Kon (1907) and by Soshestrenski (1908).

Lymphomata are evidently the commonest tumors of fowls and have occurred 7 times among 9 tumors collected by Tyzzer and Ordway (1909). Nodular and diffuse growths were seen in liver, spleen, kidneys and other organs. In one instance the tumor was said to have been associated with lymphatic leucemia. Of 19 tumors of the domestic fowl collected by Feldman (1926) 9 were "lymphocytomas" with leucemia and 2 were lympho-sarcomata.

Ellermann and Bang (1908) have described two instances of leucemia in fowls resembling very closely those described by preceding

writers In the blood they found the mononuclear cells much increased, but since the cytoplasm frequently contained granules they regarded them as myelocytes They succeeded in transmitting the disease to healthy fowls Experimental leucemia was passed from one animal to another in three generations and the changes in the blood and in the internal organs were identical with those of the spontaneous disease In a later series of experiments by Ellermann and Bang (1909) the disease was passed through 6 generations From a bird with aleucemic lymphoma they produced leucemia and reached the conclusion that the two conditions have the same cause In one instance lymphomata of the peritoneum occurring as scattered nodules had characters of lympho-sarcoma By inoculating fowls with this material they produced atypical leucemia in two successive generations

Hirschfeld and Jacoby (1909 a, b) succeeded in transmitting the leucemic disease of Ellermann and Bang through five generations and obtained leucemic and aleucemic lymphomata

Leucemia of fowls can be reproduced, according to Ellermann and Bang (1909), by a filtrate obtained by passing organ extracts through a Berkefeld filter In their first series of experiments they were successful in 2 out of 5 animals which they injected, and later were repeatedly successful with filtrates The disease may be reproduced by material filtered through Berkefeld filters (No 11 and No 12) or through Reicherts china filters

A second strain of transmissible leucemia was obtained by Schmeisser (1915) from a bird with what was believed to be myelogenous leucemia The proportion of white and red corpuscles was 1 to 13 (the normal varying between 1 to 50 and 1 to 150), large mononuclear cells were 30 per cent of the total count (normal 19 per cent) and mononuclear myelocytes with eosinophil granules were 52 per cent (normal, none) Diffuse, circumscribed, or at times nodular infiltration with myeloid cells occurred in the bone marrow, often with enlargement of the liver, spleen and kidney With suspensions prepared from the liver and spleen injected into the veins or peritoneal cavity, leucemia with characters similar to those just described was produced in 13 of 40 chickens It made its appearance after five or six weeks and was recognized by anemia, jaundice and characteristic changes in the blood Death followed within one or two weeks

Ellermann (1921a) states that young fowls are most suitable for inoculation. Greatest success has followed intravenous inoculation, injection being made into the vein of the wing just below the elbow joint. An emulsion of organs from leucemic animals is prepared in 0.9 per cent sodium chloride solution and 1 cm. is injected. Working with three strains designated A, B and C, Ellermann and Bang found that 41 per cent of the inoculated animals became leucemic, Ellermann using a strain designated E, was successful in 22 per cent of his inoculations, using strains F, G and H in 26 per cent. Hirschfeld and Jacoby (1909 a, b) had 45 per cent of their inoculations successful and Schmeisser 33 per cent.

Ellermann (1921 a, d) has observed with his strains that the duration of the disease is shortened by repeated transfer from one animal to another but that the number of animals affected is not increased. The average duration of life after the first inoculation has been about five months, in the second generation four months, and, constantly decreasing, in the sixth generation only one month. Similar results have been obtained with two other strains.

In his monograph Ellermann (1921b) describes the diseases of the hematopoietic system which occur spontaneously in fowls and are reproduced by inoculation. Leucemia may be present or absent. When lymphoid tissue is affected he designates the condition lymphatic leucosis. When the granular leucocytes and their precursors are chiefly affected he designates the disease myeloid leucosis. In birds he believes that precursors of the erythrocytes, at a stage preceding the formation of hemoglobin, may enter the circulating blood in great number and produce a condition resembling leucemia. He gives it the name erythro-leucosis. He describes in detail all of these disturbances and discusses the relation of one to the other.

Lymphatic leucosis which Ellermann (1921b, 1922) produced in fowls by inoculation is unaccompanied by leucemic changes in the blood. Anemia usually makes its appearance before death. Lymphoid infiltration, often evident as grayish white spots, occurs in the liver, spleen, kidneys, bone marrow and occasionally in the thymus, intestine and peritoneum. The newly formed lymphatic tissue is composed of large and medium-sized cells with the characters of the lymphoblasts found in the germinal centers of lymph nodes, mitotic

division is often seen. Hyperplasia of lymphatic tissue may form tumor-like masses in certain organs especially in the liver or spleen. Occasionally the new growth is so definitely localized that the term leucosarcomatosis has been regarded as applicable by Ellermann.

Disease characterized by hyperplasia of tissues concerned in the formation of granular leucocytes and designated by Ellermann (1920, 1921b) myeloid leucosis may occur with or without leucemia. In the leucemic variety the leucocytes may number from 200,000 to 600,000. Myelocytes with large granules are numerous but much more abundant are large cells with no granules and with palely-stained nuclei exhibiting every transition from the spherical to the lobed form of the polynuclear leucocyte. Ellermann believes that these cells, though usually called myeloblasts, are not normal prephases of myelocytes, but that under the influence of the virus of fowl leucemia they simulate the development of polynuclear leucocytes without forming any of their characteristic granules. The animal usually dies eight or ten days after the appearance of leucemia, at autopsy the liver is often twice its normal size and the spleen is enlarged from two to four times. In the liver there is massive infiltration, chiefly with myelocytes, having its origin in the periportal connective tissue, non-granular cells are less numerous. Similar infiltration occurs between the tubules of the kidney but is rarely seen in the spleen. Hyperplastic changes in the bone marrow are not conspicuous. In the blood vessels of the internal organs are found cells similar to those of the peripheral circulation.

In one instance of leucemic myelosis tumor-like nodules composed in great part of myelocytes were situated within the periosteum of the pelvis. The lesion suggested the chloroma of man.

In some cases of myeloid leucosis non-granular cells with lobed nuclei resembling those of the polynuclear leucocytes are predominant in the blood, in the bone marrow and in cellular infiltrations of the liver and spleen. Ellermann names them poikilonuclear cells and regards them as pathological polynuclear leucocytes. Transitions are encountered from these to cells with incompletely lobed nuclei with a few rod-shaped granules, and finally to typical polynuclear cells with abundant granules.

Another type of cell designated lymphoidocyte is occasionally seen



in the blood in the myeloic type of leucosis and has been constantly found by Ellermann (1921 b, c) in the peculiar type of avian leucemia called by him "intravascular lymphoid leucosis" These lymphoidocytes are large non-granular cells with large round nuclei and a narrow zone of basophil cytoplasm Ellermann believes they are prephases of erythrocytes for the following reasons every transition from lymphoidocytes to erythrocytes is found, lymphoidocytes occur where erythrocytes are in process of formation, unlike myelocytes and lymphoblasts they form no extravascular infiltrations, and unlike these cells but like erythrocytes occasionally have two nuclei

Ellermann means by "intravascular lymphoid leucosis" a condition characterized by anemia and by the presence of lymphoidocytes in the blood In the peripheral circulation lymphoidocytes may form 70 per cent of the leucocytes They accumulate in great number in the capillaries of the liver and spleen which are much enlarged There is similar accumulation of cells in the sinuses of the bone marrow and atrophy of the trabecula. There is no extravascular infiltration of internal organs by these cells Ellermann believes that the disease has attacked the erythrocytic system causing anemia by destruction of erythrocytes and regenerative changes with formation of prephases of erythrocytes in great number

Myeloic leucosis, lymphatic leucosis and intravascular lymphoid leucosis, which is designated erythroleucosis, are produced by the same virus and, Ellermann (1921b, 1923) states, may all appear in a series of animals inoculated with one strain of the virus The frequency of the three forms has been as follows: erythroleucosis, 69 per cent, myeloic leucosis, 18 per cent, and lymphatic leucosis, 13 per cent Furthermore, the inoculated animals occasionally exhibit pure anemia with no leucocytosis Though the lymphatic leucocytic or erythrocytic group of cells may be chiefly affected all may be implicated in some degree so that mixed forms occur In the three forms of leucosis there is a greater tendency to produce undifferentiated cells than in human leucemia

It is noteworthy that leucocytosis caused by bacterial infection may be much more intense in birds than in mammals V A Moore (1896) has described what he designates infectious leucemia in fowls caused by both spontaneous and experimental infection with a microorganism

named by him *Bacterium sanguinarium*. The leucocytes are increased to 100,000 or 200,000, the predominant type being the polymorphonuclear leucocyte with spindle-shaped granules, and no changes in blood or internal organs resembling those of leucemia are observed.

The view that the disease of fowls which resembles human leucemia is a slowly progressive avian tuberculosis has been supported by Burckhardt (1912). It is worth remarking that his experiments were made with material from an animal inoculated by Jacoby with a strain of leucemia obtained from Ellermann, and that Jacoby later found that his stock was heavily infected with avian tuberculosis. Burckhardt states that all of the animals which he inoculated had the usual form of avian tuberculosis and he admits that he reproduced in no instance the typical changes of fowl leucemia described by Ellermann and Bang. Nevertheless, it is evident that after inoculation with pure cultures of the avian tubercle bacillus, there is an increase of white cells to between 100,000 and 200,000 and occasionally to 350,000. The polynuclear cells with spindle-shaped granules are chiefly affected and young forms of granular leucocytes including myelocytes may appear in the circulating blood, but cells of lymphoid type are decreased in number. In the so-called leucemia of fowls, on the contrary, Burckhardt says, cells of the lymphoid type which are in large part prestages of leucocytes or of erythroblasts are more abundant and anemia is more conspicuous. There is, he notes, no resemblance between the lesions of avian tuberculosis and the lesions of the internal organs observed in association with leucemia. He has evidently had no opportunity to make an exact comparison between the two conditions which he has discussed and his opinion that avian leucemia is a slowly progressive tuberculosis is not supported by any convincing observations.

No evidence of the identity of leucemia of fowl and avian tuberculosis has been found by Hirschfeld and Jacoby (1912). In tuberculosis there is hyperleucocytosis which may reach a very high grade but which has no close resemblance to the blood changes of leucemia, the lesions of internal organs are not similar. Tuberculosis follows subcutaneous injection but leucemia does not. They exposed material from the organs of fowls with both tuberculosis and leucemia to a temperature of 10°C below zero, and on inoculation reproduced

tuberculosis unaccompanied by leucemia Ellermann (1921b) says that he has succeeded in separating the virus of leucemia from the tubercle bacillus by filtering through a Berkefeld filter material from a fowl with both diseases and has demonstrated the purity of the leucemia virus by inoculation into fowls

In a brief report before the Naturforschende Gesellschaft in Freiberg Schridde (1909) questions the infectious nature of leucemia in fowls He says that the injection of extracts prepared from the normal organs of birds produces changes similar to the condition described by Ellermann and Bang, which, he maintains, is not leucemia A description of the experiments was to appear, according to Schridde, in Ziegler's Beitrage, but I have not succeeded in finding any article on the subject by the author Ellermann and Bang never observed leucemic changes following the injection of emulsions prepared from organs unless the animals from which they were obtained had been leucemic

Changes in the blood resembling those of acute leucemia have been seen by Kasarinoff (1910) in a fowl poisoned by a mixture of ricin and saponin. There was intense leucocytosis, in large part referable to the presence of a great many mononuclear non-granular cells regarded as myeloblasts, polynuclear leucocytes with spindle-shaped granules were increased in number

*Conclusions* Those who claim that changes in the blood and in the internal organs comparable to those of leucemia in fowls can be produced by bacteria and other irritants have not sustained their contention by adequate evidence Nevertheless, it may be noted that multiplication of blood cells and their precursors may be stimulated more readily in birds than in mammals

Diseases occur in fowls which resemble closely human leucemias The changes in the blood and in internal organs are similar, though not identical, differences being explainable by the wide differences between the two types of animal It is doubtful whether a disease closely resembling lymphatic leucemia of man occurs in the fowl but aleucemic lymphomata are not uncommon Transitions from lymphomatosis to a disease with much resemblance to myelogenous leucemia on the one hand, and to anemia with hyperplasia of the precursors of erythrocytes on the other, are more conspicuous than

in man The recorded evidence indicates that these various changes affecting the blood and blood-forming organs are transmitted by a single virus which is ultramicroscopic and filterable by the methods usually employed In this respect they differ from mammalian leucemias which have not been transmitted from one animal to another and appear to resemble certain malignant tumors of fowls (sarcoma of Rous)

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# A REVIEW OF THE TREATMENT OF THE LYMPHATIC LEUKEMIAS AND RELATED DISEASES ESPECIALLY BY IRRADIATION

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It is my purpose, through a review of the literature, to evaluate present methods of treatment of the lymphatic leukemias, among which are included chronic lymphatic leukemia, acute lymphatic leukemia, and aleukemic lymphoma

The histo-pathology of Hodgkin's disease, lympho-sarcoma, leuko-sarcoma and mycosis fungoides is to be briefly considered from the viewpoint of group relationships. Special attention is given to the effect of irradiation upon normal and diseased lymphatic tissue and the clinical results of its use in treatment

I shall include a brief review of the embryology, anatomy, physiology, histology and histogenesis, of normal lymphatic tissue, the essential histo pathology of lymphatic leukemia, present opinion as to the classification of lymphatic leukemia and its relations to other lymphatic diseases, the metabolic changes in leukemia after irradiation, the effect of light on lymphocytes, and the present status of the experimental production of leukemia. The technique of irradiation as practised at the present time is outlined. The results of treatment of lymphatic leukemia by agents other than irradiation are summarized

## NORMAL LYMPHATIC TISSUE

### *a Embryology*

Embryologists agree that lymph nodes do not develop in man until the latter part of the third month. The endothelium forming the lymph vessel originates as an off-shoot or bud from the endothelium of a vein. After a plexus of such lymph vessels is formed, the embryonic

lymphocytes begin to collect and multiply around the lymphatics. These cells are either differentiation products of the connective tissue cells (mesenchymal) *in situ* or have migrated to this position through the walls of neighboring blood vessels.

Both the spleen and the lymph nodes are of mesodermal origin. At one time the spleen was thought to be derived from the epithelium of the gut tube, but in the light of recent work this theory has become untenable. Save for the replacement of lymph sinuses by blood sinuses as in the spleen, the hemo-lymph nodes originate in the same way as lymph nodes.

Flemming (1884-1885) suggested that the lymphocytes of the cords were produced by the germinal center cells. His theory has been generally accepted, but certain histologic observations cast doubt upon it. The difference in morphology and staining is well known. Germinal centers are not found in certain lymph nodules, and are absent from the medullary cords. They are also absent from the early stages of embryonic nodes.

### *b Anatomy and physiology*

It is not the purpose of the present article to go deeply into the anatomy and physiology of lymphoid tissue, but only to note certain salient points in relation to the studies in hand.

From the anatomical arrangement of lymphatic tissue, it appears to have a part in the protection of mucous membranes. The mucous membranes of the mouth, the tongue, the nasal passages, the bronchi, the esophagus, the stomach, the intestine, the bladder and urethra, have almost invariably a submucosal layer containing lymphocytes in great numbers, arranged with or without germinal centers.

The salivary glands, the thyroid, the liver, the pancreas, the kidneys, and the adrenals do not normally contain much lymphatic tissue within their interstices. The lymphatics of the lungs and bronchial tubes drain into a group of nodes about the hilus of the lungs and around the tracheo-bronchial junction. The lymphatic tissue of the abdominal cavity, aside from that beneath the mucosa of the gut tube, is collected into three main lymphatic structures or sets of structures, the spleen, the mesenteric lymph nodes, and the posterior peritoneal nodes. The deep pelvic nodes are situated along

the large vessels and, together with the inguinal groups, receive lymph from the genital organs and lower extremities

The hemo-lymph nodes are thought to have a structure and function similar to splenic tissue. They are directly in the course of blood vessels instead of lymph vessels. Their sinuses, therefore, are filled with blood instead of lymph (Mottram, 1923, Jordan, 1924). They are found in the retroperitoneal fat and the prevertebral region of the neck.

### *c Histology*

There are three cellular elements in the lymph node which are peculiar to it: the lymphoid cells, endothelial cells of the sinuses and perivascular spaces, and the reticulum cells and fibers. There are constantly present, also, structures which belong to the so-called myeloid series, polynuclear neutrophils, and eosinophils, and large mononuclear cells like the formative cells of the bone marrow. Cells of these three types are doubtless deposited by the circulating blood.

Certain observers have wished to see myeloid tissue in lymph nodes, and thus explain the presence of such cells upon the basis of local production. Since, however, the diseases of lymph nodes never express themselves with alteration of myeloid cells but only of lymphoid cells, and since myeloid alterations are definitely associated with bone marrow changes, it is not necessary, for our purpose, to discuss further academic questions concerning the existence of differentiated marrow cells in the lymph nodes. When polynuclear cells are present, there is usually other evidence of inflammation, and when myelocytes and promyelocytes are found, they can be explained by other lesions of bone marrow disease.

In the spleen the malpighian bodies are composed of germinal center cells and so-called adult lymphocytes, arranged as the cells of the lymph nodes. In the red pulp, the connective tissue forms a thick network, in the meshes of which lie the parenchyma of the spleen and the sinus spaces. The cellular elements of the reticulum are macrophages.

Von Ebner (1902) distinguishes the varieties of pulp cells according to their morphology without reference to their origin, as (1) small mononuclear lymphocytes, (2) mononuclear, polymorphonuclear and

multinuclear leucocytes, (3) nucleated red blood cells, (4) adult red blood cells (5) large phagocytic cells, enclosing red blood cells or pigment granules; and (6) megacaryocytes, or giant cells with polylobular nuclei appearing only in young animals. Blood platelets and free pigment granules occur. The leucocytes (2) are in the majority, the lymphocytes (1) are next, and the phagocytes (5) next. It is thus seen that the spleen contains all the cells present in the lymph node, and in addition certain cells peculiar to itself, which have been said to originate in the malpighian follicles.

It is evident that the different regions of the spleen have different functions, and this opinion is supported by the observation that exposure of rats to the roentgen ray first destroys the cells of the follicles and leaves the pulp elements unchanged until after much longer exposure. The different reactions of pulp and follicle in the leukemias also support this theory. In myeloid leukemia, the pulp is said to show hypertrophy, whereas in the lymphatic form the follicle shows hypertrophy (Kahn, 1923).

#### LYMPHATIC LEUKEMIA

##### *a Group synonyms and classification*

Wunderlich coined the term malignant lymphoma. It is a present fashion to use it in a collective sense to cover the group of progressive, ultimately fatal, diseases affecting primarily the lymphocytes and lymphatic tissue. Its derivation suggests a new growth. Whether Hodgkin's disease should be included, and whether lympho-sarcoma, lymphatic leukemia, and aleukemic lymphoma are variants of the same disease are questions which have vexed pathologists for 75 years. In the meantime the struggle over classification has evolved the following formidable list of terms, historically interesting, but confusing: progressive multiple lymph gland hypertrophy (Wunderlich, 1858), lymphosarcoma (Virchow, 1864-1865), pseudo-leukemia (Cohnheim, 1865), ademie (Trousseau, 1865), multiple lymphadenoma without leukemia (Wunderlich, 1866), malignant lymphoma (Wunderlich), Hodgkin's disease (Wilks, 1865), lymphatic leukemia (lymphocytic and lymphoblastic), aleukemia (Pappenheim, 1907b), aleukemic lymphatic leukemia, leuko-sarcoma, aleukemic lymphadenosis

(Schridde), lymphomatosis, round cell sarcoma, aleukemic lymphoma, lymphadeno-sarcoma, Mikulicz's disease, mycosis fungoides, and lymphoblastic erythrodermia (Sequeira and Pantón, 1924-1925)

For the purposes of clear indexing the following terms seem desirable

- 1 Lymphatic leukemia
- 2 Aleukemic lymphoma
- 3 Lympho sarcoma
- 4 Hodgkin's disease
- 5 Leuko sarcoma

### *b History*

The history of the disease leukemia extends over a period of 81 years. Hughes Bennett (1845) recorded a peculiar case of suppuration of the blood with enlargement of the liver and spleen. He called the disease "leucocythemia." In the same year, but a little later, Virchow (1845) described a condition which he named leukemia. Eight years later Virchow (1853) drew a distinction between splenic and lymphatic leukemia. The clear-cut differentiation of leukemia into the two types, myelogenous and lymphatic, followed the newer staining methods perfected by Ehrlich (1891).

In 1895 Roentgen discovered the x-rays. Roentgen-ray therapy in leukemia was used first in 1901 by Pusey (1902) and by Senn (1903). M and Mme Curie discovered radium in 1898. Its value in the treatment of leukemia was reported in 1914 (Rénon, Degrais and Tournemelle, 1914) and 1915 (Pinch, 1915). Deep x-ray therapy was described by Dominici (Wickham and Degrais, 1910) and elaborated by Kroenig, Gauss, and others.

### *c Histopathology of chronic lymphatic leukemia*

The peculiar histological picture of chronic lymphatic leukemia is best seen in an excised lymph node. The architecture of the node is as a rule completely destroyed. The orderly arrangement of germinal centers, cords, sinuses, and fibrous septa is replaced by an unorganized hyperplasia of lymphatic cells. The uniformity of cell type is striking and there is usually little variation in the size and appearance or intensity of staining. The effect is as if a given cell

had continued to form new cells of its own type unrestrained by the usual barriers until the entire node consisted of a monotonous repetition of uniform cells

Wherever lymphatic tissue normally occurs the same histological picture is seen. The hyperplasia of lymphatic cells is general. The spleen, the superficial lymph nodes, the submucosal collections of cells in the gastrointestinal tract, the lymphatic tissue of the bone marrow, the lymphatic tissue about the bile ducts, the tonsils, the thymus, the peribronchial nodes, subcutaneous collections of lymphatic tissue, all show the unorganized hyperplasia of the same cell type. Occasionally slight evidence of inflammation is seen but as a rule there is no indication of fibrosis, polynucleosis, endothelioid cell reaction, or other granuloma-like features.

The capsule of the lymph node and the structures about the lymph node are usually not invaded by the lymphatic cells as by an infiltrating new growth. The capsule may however contain a few of the abnormal cells. Accompanying this pathological picture there is an increase in the lymphocytes of the blood.

#### *d Aleukemic lymphoma*

The histological features of the excised node are the same as in lymphatic leukemia. The only difference is the absence of the peculiar blood picture. Although there may be no increase in the absolute number of circulating leucocytes there is usually an increase in the relative number of lymphocytes in the differential count—the so-called sublymphemic blood picture. Many observers prefer the term the aleukemic phase of leukemia, and object to the classification of aleukemic leukemia (aleukemic lymphoma) as a separate and distinct disease. An aleukemic state may occur in both chronic and acute lymphatic leukemia. In the latter it sometimes appears as a sign of exhaustion, the drop in circulating lymphocytes increasing as the patient becomes weaker and approaches death. The aleukemic phase can be produced by irradiation in a patient with chronic lymphatic leukemia.

In acute lymphatic leukemia the peculiar hyperplastic picture in the lymphatic tissue may be lacking or may resemble closely the histology of the chronic disease although the cells appear to be of a more im-

mature type All grades of hyperplasia occur between the two extremes The cell type in acute lymphatic leukemia is usually the large immature lymphocyte Without oxydase stains it is often impossible to distinguish it from immature myeloid cells The cell type in chronic lymphatic leukemia in the circulating blood usually resembles a normal adult lymphocyte, while in the fixed lymphatic tissue the cell resembles the cells of the normal germinal centers

DEFINITION AND BRIEF DESCRIPTION OF CERTAIN DISEASES SOMETIMES THOUGHT RELATED TO LEUKEMIA

*a Lympho-sarcoma*

Virchow (1864-1865) applied the term lympho-sarcoma to a group of diseases involving the lymphoid apparatus which included Hodgkin's disease, what is classified to-day as aleukemic lymphoma, and lympho-sarcoma Kundrat (1893) drew the distinction, now accepted by most authorities, between lympho-sarcoma and other lymphatic diseases He designated a growth of lymphoid tissue, somewhat more restricted locally than in Hodgkin's disease, or in leukemia, having greater invasive tendencies suggesting sarcoma, but lacking marked evidence of metastasis by the blood stream

*b Leuko-sarcoma*

The term leuko-sarcoma has been given to those cases which show the local characteristics of lympho-sarcoma together with an increase in the circulating mononuclears of the blood They seem to stand between lymphatic leukemia and lympho-sarcoma

*c Mycosis fungoides*

This disease was first described by Alibert in 1814 It has been placed among the granulomas by Stellwagen, Auspitz, Hatch, and others, among the pseudo-leukemia and lympho sarcoma group by Paltauf, and among the leukemias It is impossible to say at the present time what its proper classification is

*d Hodgkin's disease*

The histological difference between Hodgkin's disease and lymphatic leukemia is the granuloma-like appearance of the specific lesion of



Hodgkin's disease, i e , fibrosis, the presence of numbers of polymorphonuclear cells and endotheloid cells, sometimes with areas of necrosis, and the absence of features peculiar to leukemia Hodgkin's disease begins as a local condition and spreads to neighboring lymph node areas Lymphatic leukēmia apparently involves all the lymphatic tissue simultaneously The one is a local disease which spreads, the other is a general disease from the beginning

### *e Mixed leukemia*

The oxydase granule staining method as modified by Graham (1916) has explained many of the so-called mixed leukemias, that is, leukemias said to have increase of both myeloid and lymphoid cells in the blood of the same patient. It has shown that with ordinary staining methods the premyelocytes often appear morphologically similar to lymphocytes of immature type. In acute myelogenous leukemia, the premyelocytes may enter the circulation at such an early stage of their development that granules in the cytoplasm can not be demonstrated by any known staining method. From recent work it is probable that most cases of acute leukemia belong to the myeloid group, although infrequent cases of acute lymphatic leukemia undoubtedly occur The existence of a true "mixed leukemia" as an entity in man has never been fully substantiated.

### EFFECT OF IRRADIATION ON NORMAL LYMPHATIC TISSUE

The study of the effect of irradiation on normal lymphatic tissue has been stimulated primarily by the favorable results obtained in the treatment of leukemia with x-rays, and recently by the study of resistance to cancer These studies have been reported especially from the Middlesex Hospital, London, by Mottram and Russ (1919-1920, 1921) and by Russ, Chambers, Scott and Mottram (1919), and from the Rockefeller Institute, New York, by Murphy and Sturm (1919), Murphy and Nakahara (1920), Nakahara and Murphy (1921), Murphy, Liu and Sturm (1922).

Heineke (1904) first emphasized that lymph cells are peculiarly susceptible to roentgen rays He demonstrated in small animals that x-ray exposures primarily affected the lymphatic tissue Degenera-

tion of the lymphoid follicles in the spleen and lymph nodes and a drop in the number of circulating lymphocytes developed. Several days after irradiation the lymphocytes almost entirely disappeared while the absolute number of polymorphonuclear cells and large mononuclears showed very little change.

Aubertin and Beaujard (1908) were the first to report that after x-ray treatment a primary leucocytosis developed, and afterwards a leucopenia. The leucocytosis was due to an increase in polymorphonuclear leucocytes. This observation has been confirmed by many others, among them Taylor, Witherbee, and Murphy (1919). Apparently the height of the leucocytosis is different in man and in animals, in animals the number of leucocytes may be doubled, in man an increase of more than 50 per cent is unusual.

The initial leucocytosis generally lasts about 24 hours. It begins about 2 hours after the treatment and reaches its height about 12 hours after treatment. When radium is used the leucocytosis lasts as long as 48 hours. The effect of x-rays and radium is essentially the same, but there appear to be some slight differences in the degree and intensity of reaction. For instance Levin (1922) thought that radium caused less general disturbance to the blood and hematopoietic system than corresponding doses of roentgen rays.

Linser and Helber (1905), after numerous experiments with animals, concluded that x-rays destroy not only the lymphoid cells of the spleen and nodes, but also the circulating leucocytes, especially the young lymphocytes. They reported also that following x-ray treatment a new substance, a leukotoxin, was produced in the blood which destroyed the circulating leucocytes, especially the lymphocytes. The presence of such a leukotoxin has not been fully substantiated. Murphy and his coworkers at the Rockefeller Institute were unable to prove such a substance in the serum of x-rayed rats.

David and Desplats (1912) confirmed the work of Heineke and extended it. Their experiments indicated that the roentgen rays have a selective action on lymphoid, myeloid and endotheloid cells, causing nuclear disintegration, fatty degeneration, and necrosis, which may be followed by secondary fibroblastic or endothelial proliferation. In small animals they find that a very short exposure may cause changes nearly as marked as much longer exposures, or the changes

may be slight, or in direct proportion to the degree of exposure. Sex, age, species, and individuality were also factors in determining the effect of roentgen rays. White rats were more sensitive than white mice, male rats than females, young ones than old ones. The individual resistance also varied.

Exposures of five hours or more killed mice, rats, young rabbits and guinea pigs in from two to ten days. The symptoms leading to death were uniform and characteristic, and probably to be interpreted as an intoxication resulting from the disintegration of cell-protein. The greater the destruction of lymphoid tissue, the more conspicuous the symptoms of intoxication. By prolonged exposures practically all the lymphoid tissue of the spleen may be destroyed. The destruction of lymphoid tissue was always more extensive in the spleen than in the lymph-glands or bone-marrow. Exposures producing the appearance of chromatin dust in the spleen had a slighter effect upon the mesenteric glands. David and Desplats explain this result by the assumption that the white cells in the spleen are in a more unstable condition.

The cells chiefly affected by the roentgen rays were the young forms, the small and large lymphocytes, and the myelocytes. Fewer of the polymorphonuclear leucocytes were destroyed. Regeneration of lymphoid tissue was slow after prolonged or repeated exposures, especially after destruction of the younger forms. They think that changes in the large epitheloid cells in the follicles after intense exposure may explain the slow regeneration.

Fox and Farley (1923) summarized the effects of irradiation on lymphoid tissue as follows:

Mild doses playing upon lymphatic tissue cause low-grade hyperplasia in cords and follicles while protracted or repeated exposures are followed by a diminution of small mononuclears. After the reduction of the normal lymphocytes from repeated irradiation, larger cells develop resembling the normal lymphoblasts in appearance. They seem to act as lymphoblasts. These cells are somewhat resistant to the action of the x-rays. If radiation of normal nodes be not too prolonged, for example to the extent of fibrous tissue stimulation, normal architecture and histogenesis will probably return. The stage of degeneration in lymphatic tissue is demonstrated by swollen or vacuolated cells, in pyknotic or fragmented nuclei and by

"chromatin dust" Reactive phenomena take the form of an increase of the lymphoblasts noted above, a prominence of endothelial cells and later connective tissue overgrowth, both of the latter two seem stimulated by x-ray directly or by the degeneration products of cellular death. The endothelial cells, because of evidence of phagocytosis in them and because they seem to multiply during treatment have been thought to participate not only in the removal of cellular debris, but actually to affect the destruction of lymphocytes.

David and Desplats (1912) believe that irradiation is effective while the endothelial cells are still active, and that when fibrosis is excessive and chokes them out of existence the favorable effects of irradiation cease. Connective tissue increase is usually explained as a process which is reparative as well as due to stimulation by the rays. In addition to the above changes there may be intravascular endothelial hyperplasia or blood coagulation or both, with the resultant destruction of the lumen of vessels, depriving some sections of tissue of nutrition. In view of these changes it is not difficult to imagine that normal anatomy of lymphatic tissue does not return after x-ray treatment of hyperplasias, tumors, or inflammations.

Murphy and Morton (1915) found that large doses of x-rays destroy lymphoid tissue and that small doses after causing a certain amount of destruction, bring about an actual stimulation of lymphatic tissue. The most satisfactory stimulation was obtained with x-rays of comparatively long wave lengths and therefore of low penetrating power. Murphy, Liu and Sturm (1922) found that the serum of x-rayed normal rats caused an increase in the number of lymphocytes "in vitro". In two hours it amounted to 15 to 30 per cent. There was also an increase in mitotic figures. In their experiments they prepared lymphoid cells from the thymus and lymph glands of rats, suspended them in the serum of x-rayed rats, and incubated them for two hours. A like suspension of cells in normal serum underwent rapid disintegration and in only one instance among a large number of films examined was a mitotic figure found. The stimulative effect of serum from x-rayed rats endured from one to two hours after the exposure but was not detectable in the serum taken seventeen hours or more after the treatment. Serum x-rayed "in vitro" was devoid of stimulative action. It would appear, therefore, that the change is not a simple

one in the serum itself. Furthermore, it is known that the stimulation of lymphocytes induced by x-rays "in vivo" is always preceded by some destruction of lymphoid cells, a circumstance suggesting that the stimulating substance may be a disintegration product of lymphoid cells. Furthermore, the experiments of Murphy and his co-workers failed to show any evidence of a so-called lympho-toxin in the serum of x-rayed animals, even after an exposure so long as to cause almost complete destruction of the lymphoid tissue of the living animals.

Murphy discusses the complicating effect of foreign protein, and the instability of the blood counts of rabbits and guinea pigs, as possibly accounting for the results of these early experiments.

Schinz (1924) showed that the cell nucleus is most sensitive to irradiation when undergoing mitosis. If the cell can also be stimulated to mitosis by mild irradiation, the question arises whether a preliminary mild treatment followed by a more destructive dose at the proper time might not be more effectual where destruction of tissue is the object.

Holthusen (1925) and Spurling and Lawrence (1925) have demonstrated that cells in the blood are more resistant to irradiation than the same cells in the sites of formation. Menetrier and Touraine concluded from experiments that x-rays are especially active in destroying young cells in active proliferation (quoted by David and Desplats, 1912).

#### EFFECT OF X-RAY UPON THE HISTOLOGY OF LYMPH NODES AS SEEN IN NODES REMOVED FROM PATIENTS WITH LYMPHOADENOPATHY

The foregoing summary is largely from work of experimental character. There have been very few reports of direct histological examination of lymph nodes removed at biopsy after roentgen ray treatment.

Laignel-Lavastine and Coulaud (1922) describe a case of Hodgkin's disease in which the first biopsy showed recent sclerosis in strands especially near the periphery, many polynuclears arranged in small groups, numerous young connective tissue cells, many eosinophiles, and a moderate number of very large cells of unusual shape with multiple nuclei (Reed cells), some arranged peripherally. Thorough x-ray

treatment was made over the enlarged nodes. They decreased rapidly in size, with marked clinical improvement. A second lymph node was removed six weeks after x-ray treatment. Microscopically it was almost entirely sclerotic, but the connective tissue was so active that it resembled sarcoma. Polynuclears were absent and only a few transitional forms and eosinophiles were present. There were none of the very large cells with multiple nuclei. Plasma cells were numerous in the connective tissue areas. The outstanding changes were the rapid fibrosis and disappearance of the large nucleated cells.

Fox and Farley (1923) reported seven cases in which a node was removed before and after x-ray treatments, and the histological differences were studied. The group included 2 cases of Hodgkin's disease, 1 case of Sternberg's pseudo-leukemic tuberculosis, 2 cases of aleukemic lymphoma, 1 case of leukemia cutis with sublymphemic blood, and 1 case of lympho-sarcoma. From the histological changes after x-ray it was possible to place the cases in three groups.

- 1 The lymphogranulomatous (Hodgkin's) nodes clearly showed fibrosis, and disappearance of the endotheloid and giant cells. The lymphoid cells disappeared almost entirely. The reaction as a whole resembled the coarse and deforming fibrosis seen in late stages of tumor-forming Hodgkin's disease. The general aspect was as though the natural course of events within the node had been accelerated.

- 2 The most striking difference of the leukemic group from the granulomatous group was the practical absence of fibrosis. Small adult lymphocytes appeared to be reduced in number. The large vesicular mononuclears seemed actually to be increased in number. Vascularity of the node was greater after treatment.

- 3 In the case of lymphosarcoma, the cellular picture which primarily was almost homogenous, was changed by x-ray into one in which degenerated cells were mixed with actively growing individuals resembling spindle cell sarcoma elements. The fibrosis was increased in strands and between units, but not to the extent seen in the granulomatous group. Obliterative thrombosis was not notable in any of the sections made after x-ray treatments. The degree of irradiation and the number of treatments necessarily varied with the patients, thus making impossible absolute conclusions from comparison.

## CHEMICAL METABOLISM AFTER IRRADIATION IN LEUKEMIA

Knudson and Erdos (1917) found the excretion of total nitrogen, urea, ammonia and phosphates very greatly increased after irradiation over the spleen in myelogenous leukemia. The uric acid output was raised but slightly in comparison with the other nitrogenous elements. Their interpretation was that the application of radium over the spleen accelerates the disintegration of nuclear material. Uric acid, which one would expect to be increased from the breaking up of nuclei, is probably broken down further and excreted as a different product. There was an especial increase in the phosphates, at times as much as 400 per cent.

Studies of blood phosphorus in myelogenous leukemia were made by Buckman, Daland and Weld (1925). They found an elevation of the phosphorus content of the blood, due to an increase in the phosphorus content of its formed elements and not of the plasma. They concluded that the immature myeloid cells especially are rich in phosphorus and that the phosphorus content is an index of their maturity.

Gunderson (1921) concluded that the increased metabolic rate in leukemia is also an index of the degree of immaturity of the white blood cells. It is known that young cells in general have a higher rate of metabolism than older cells. Buckman and others thought the total phosphorus content of the corpuscles to be a more sensitive index of their immaturity than the patient's basal metabolic rate. After roentgen ray therapy a transient increase of the total phosphorus content of both plasma and cells generally occurs as a result of tissue destruction. The cells seem to act as a temporary reservoir for the phosphorus thus suddenly increased in the plasma. This change after roentgen ray treatment occurs in both leukemia and cancer but to a much greater degree in leukemia, no doubt because of the greater destruction of immature cells in that disease. After the initial disturbances following a successful roentgen ray treatment in myelogenous leukemia, the total corpuscular phosphorus subsides to normal levels, probably because the immature cells have been disposed of. When the patient relapses and immature cells increase in the blood, the total blood phosphorus again rises. No significant changes were

noted in the inorganic phosphorus before or after irradiation in leukemia and cancer. The studies were made on myelogenous leukemia but it is to be expected that corresponding changes occur in lymphatic leukemia.

All possible means of guiding irradiation therapy in leukemia are welcome since the questions of when to stop treatment and when to begin are not readily answered.

#### THE ACTION OF LIGHT ON LYMPHOCYTES

The study of the effect of light on the lymphocytes has been carried out almost entirely by observations on the lymphocytes of the blood.

Most of the experiments have been occupied with the effect of sunlight. It should be realized that such studies are concerned both with rays of the visible spectrum, that is, rays having wave lengths of from 400 to 760 millimicrons, and with the invisible rays above and below the range of the visible. These include the infra-red, having wave-lengths above 760 millimicrons, and therefore above the visible range, and the ultra-violet, having waves of from 100 to 400 millimicrons, and therefore below the visible range.

Polito (1908) exposed rabbits to direct sunlight for varying periods. He found an increase in the total count consisting largely of increase in the mononuclear cells. The increased counts amounted to as much as 5000 per cubic meter. After an hour the blood returned to normal. Murphy and Sturm (1919) have shown that dry heat produces an increase in the circulating lymphocytes of the blood. It is uncertain what part changes in blood volume and changes in the peripheral capillary bed played in the results reported in these experiments. Aschenheim (1913), Taylor (1919), Wickline (1908) and others have reported increase in lymphocytes after exposure to sunlight. There is considerable evidence that residents of tropical countries have a higher total of lymphocytes than residents of temperate zones. These studies have been made by Guerrero and Sevilla (1909), Phalen (1910), Wickline (1908) and others.

One of the best controlled studies, considering the type of ray, has been reported by Janet Howell Clark (1921). An iron arc was used by Clark. It gives out rays from 650- $\mu$  to 238 millimicrons in wave length, that is, rays below the visible spectrum in the ultra-violet



range, and rays above in the infra-red range Heat was eliminated by distance By means of filters of different colored glass, picric acid, etc., the range of the rays used in the exposures was controlled She concluded that the region of far ultra-violet (wave lengths shorter than 300 millimicrons) has practically no effect on the absolute number of polynuclears of the peripheral blood, but produces a very marked lymphocytosis, lasting about 3 weeks. The near ultra-violet (330 to 390 millimicrons) has a depressing effect on lymphocytes and, to a less degree, on the polynuclear cells The region between 450 and 650 millimicrons has a stimulating action on both lymphocytes and polynuclears, especially on the former

POSSIBLE EXPERIMENTAL PRODUCTION OF LEUKEMIA, RELATION  
TO RADIO-ACTIVITY, ETC

Leukemia has been reported as occurring naturally in animals Much study has been made of the disease in fowls The nucleated red blood cells of the fowl, and the differences in leucocytes from those of man have offered considerable difficulty The experimental production of the disease in large animals would be a decided advance. Sternberg (1912) states, "As for the cause of leukemia the only interesting observation is that of Ellermann and Bang on the transmission of leukemia in the fowl by the filtrate of organs, and transfer by Ludke (1910b) of marrow and spleen from a mixed leukemic dog to another dog An acute leukemic picture may be produced by pyridin and toxins of some cocci " The mention of the acute leukemic blood picture in the last sentence refers to the work of Ludke in 1910 Ludke, using dogs and apes, first brought about a marked anemia with pyridin When emulsions of streptococci and staphylococci were then injected intravenously into the prepared animals, a picture somewhat resembling acute myelogenous leukemia was produced in the blood However, as Sternberg says (1912), the results obtained were not analogous to myeloid leukemia in human beings They were more like a symptomatic myelocytosis, and proof is lacking of a toxic-infectious cause of the disease Sternberg (1911) refers to his own work with streptococci along this line in which he confirmed the work of Ludke but failed to find that a true leukemic blood picture was produced Zeigler (1906) effected a myelocytic blood reaction

in animals by means of large doses of x-rays over the spleen. His explanation was that the damaging action of the x-rays on the Malpighian follicles of the spleen disturbed a hypothetical mutual inhibitory action existing between the lymphoid and myeloid systems.

A number of cases of aplastic pernicious anemia in workers with radium, x-rays and thorium have been reported. Émile-Weil (1925) observed recently two civil engineers who had been working in the same laboratory preparing radio-active substances of the thorium group, one of whom succumbed to pernicious anemia and the other to myeloid leukemia. He cites from the literature seven other cases of leukemia that developed under similar conditions. Five of the seven developed in x-ray workers, one in a person who handled radium, and one in a person who received x-ray treatment. In 7 cases the leukemia seemed to be produced by small doses of rays over a long period of time. In the one case of therapeutic origin the patient received a single massive dose of penetrating rays for uterine fibroid. However, the leukemia did not develop until four years later, and there seems to be considerable doubt as to whether the rays were a factor in causation. He states that the leukemias in these eight cases were of both the lymphatic and myelogenous types. In view of the undoubted production of aplastic pernicious anemia by the action of rays on the bone marrow, it is not surprising that the production of a myelogenous type of leukemia by rays should be reported, but the production of lymphatic leukemia by such means should not be credited without very close scrutiny.

Sellards and Baetjer (1918) inoculated splenic tissue from a case of acute leukemia in man into the spleens of cats. Death occurred promptly. Splenic tissue from these animals was injected into the spleen of a monkey (*Macacus rhesus*). A temporary leukemic blood picture was produced. The animal recovered. Attempts to transmit to a second monkey failed to have the previous result.

#### RECENTLY REPORTED RESULTS OF TREATMENT OF LYMPHATIC LEUKEMIA BY IRRADIATION AND MISCELLANEOUS METHODS

Irradiation in leukemia has been accomplished by the use of radium, the roentgen ray, mesothorium, thorium X, and various radium salts. The last three have been injected intravenously.

The results obtained by radium treatment in the past decade have been very promising. Some observers (Ordway and Gorham, 1920, Ordway, 1917) have been rather decided in their opinion that radium is superior to the roentgen ray in the treatment of leukemia. Others, more conservative, consider the older method of irradiation (with the roentgen ray) of equal value, and the method a matter of choice except when certain indications arise in the individual case. These special indications are noted in the section on technique, especially that described by Pancoast. Ordway (1917) is of the opinion that a conspicuous therapeutic result can sometimes be obtained by radium in cases which have become resistant to the x-ray. There is probably no inherent difference in the two methods.

Béclère and Béclère (1913-1914) reported excellent results from using concentrated rays over the spleen. Béclère marked out carefully a number of small portals of entry. His technique has had much influence.

Béclère summarized his observations in the treatment by roentgen ray of leukemias which included 12 lymphatic, 93 myelogenous and 5 acute. The results in the acute cases were nil. The most valuable results were obtained in those of the myelogenous type. All the lymphatic group showed improvement for a time, in increased strength, disappearance of the enlargement of the lymph nodes and spleen, diminution of the anemia, increased appetite and a sense of well being.

He considered that the best results came from direct treatment of the spleen in myelogenous leukemia and of the lymphatic masses in the lymphatic type. Like many others, he reports that he could not see notable effects from attempted raying of the bone marrow. Roentgenologists are divided upon the value of raying the long bones, but most of them do so in addition to raying the spleen and lymphatic masses. Some have made the mistake of raying the shafts of the bones rather than the extremities where most of the red marrow is located. The bone marrow of the shaft of the long bone is largely fat, and no result on the myelocytes and lymphocytes should be expected with such technique. Béclère attempted to follow the blood picture carefully in the interval following treatment, and to reinstitute treatment when the blood indicated a relapse. In aleukemic lym-

phoma it is necessary to judge recurrence by the return of the lymphatic masses since the blood gives no indication, except in those cases, not infrequently observed, which pass from a state of aleukemia to a frank leukemic blood picture

The course of acute leukemia of both types, myelogenous and lymphatic, is not shortened by the use of radium or x-rays. In some cases it has seemed to do harm and to hurry the patient on to a fatal ending

All (Minot and Isaacs, 1924, and Wood, 1922) agree that leukemia of the chronic type is benefited by irradiation. No cures are reported. Although most authorities consider the improvement temporary, it is often striking. The patient who has been a semi-invalid rapidly gets better, all signs of the disease disappear, and apparently he is entirely well, able to pursue his occupations and enjoy life. The duration of his freedom from symptoms is variable, and appears to depend upon factors concerning which we know little. The disease seems to have a fixed rate of progress. Some patients live for 2 years, others for 15 years, before it is fatal. The duration and rate of advance seem dependent upon a multitude of imponderable factors, such as heredity, race, or resistance of the patient, conditions influencing the rate of cell division, etc. Dr Frank Billings (1922) mentions the case of a laundress with chronic lymphoid leukemia who was under observation for 12 years. She refused all irradiation and had only small doses of arsenic and iron.

Minot and Isaacs conclude from a study of their results with and without irradiation that the length of life of the patient is not markedly influenced by irradiation, but that he is able to live, while he does live, in greater comfort and freedom from symptoms.

The intravenous use of mesothorium and thorium is still in the experimental stage and no really consistent results have been reported. Wada (1925), using small intravenous injections of radium bromide, demonstrated a favorable action on blood formation, but radium was found in the marrow after several months. Such a form of therapy cannot be looked upon as desirable, for its control is too indefinite.

Falta, Kriser, and Zehner (1912) produced remission in leukemia by the injection of thorium X. Thorium X and mesothorium have also been employed by the method of application. There are no ad-

vantages over radium application, the results being almost the same. One finds reports in the literature of intravenous injections of various radioactive substances for the past 25 years. No consistent benefit has so far been proven. One of the latest reports is by Stevens (1926). A summary of the literature and a bibliography can be found in his article.

Minot and Isaacs (1924) studied the age incidence, duration, and benefit derived from irradiation in 98 cases of chronic lymphatic leukemia and 57 acute cases. Thirty cases had not been subjected to irradiation. 50 cases had been given irradiation by x-ray and radium of varying technique because of the period of time over which the treatment extended.

They found that chronic leukemia is distinctly a disease of middle life, most of the cases occurring between the ages of 45 and 55, that acute leukemia seldom occurs after 25, that the male sex is affected three times as often as the female. This preponderance in males has been noted by others. They concluded that irradiation had not prolonged life in patients suffering from either acute or chronic lymphatic leukemia. This observation has been made by other authorities. In 80 patients, over 30 years of age, with chronic lymphatic leukemia, Minot and Isaacs noted that the average duration of life after the history of the first symptom was 3.45 years. This average was practically the same in the 50 cases treated by irradiation as in the 30 cases not treated by irradiation. Such a conclusion should not be considered as generally applicable without further statistical investigation. Certainly the impression of many other observers is that irradiation prolongs life in the individual case. The duration of chronic lymphatic leukemia was longer in older than in younger persons. Approximately 14 per cent of all patients live 6 to 8 years.

In acute lymphatic leukemia the statistics of Minot and Isaacs indicated that the improvement from irradiation was evanescent and slight. About half the patients died in less than two months after initial symptoms. In the chronic form, on the other hand, there was undoubted symptomatic benefit from irradiation. In 47 per cent of 61 chronic cases general improvement occurred. There was slight improvement in 30 per cent and no improvement in 23 per cent. In 10 per cent there was striking increase in well being and efficiency.

The number of white cells in the blood did not indicate the patient's true condition so accurately as the morphology of the lymphocytes, the number of blood platelets and the percentage of hemoglobin. When the hemoglobin was less than 50 per cent irradiation usually caused little or no improvement. The same result was observed when the blood platelets were so low as to cause a secondary purpura. The more immature the circulating lymphocytes were, that is, the nearer they approached the young cells of acute leukemia, the less benefit was to be expected from irradiation. An aleukemic blood picture did not necessarily indicate improvement, since such a picture occurred in patients seriously ill. The increase in the patient's sense of well being and the decrease in the size of the lymphoid masses or spleen appeared to be proportional. Irradiation usually was successful in relieving pressure symptoms caused by enlarged lymph nodes. Exceptions to this rule, however, occurred. It is possible that a change to a different form of irradiation might be successful in resistant cases.

Minot and Isaacs believe that treatment and prognosis in the individual case should not rest upon any single item such as the blood picture, but should be guided by correlated information from history, physical signs, blood examination, and determinations of the basal metabolic rate. Irradiation became less effective as the disease progressed. This phenomenon they considered due to progressive involvement of the bone marrow. Nevertheless, irradiation seemed to be of distinct value and maintained the patient in a better state of health and efficiency than if it had not been given. As to the time that the benefit from a course of irradiation may be expected to endure, they state that it often persisted for three months, rarely a year, while in advanced cases slight improvement often lasted for but a few weeks.

As for prognosis in exceptional cases, Minot and Isaacs record the interesting fact that they have under observation at present 5 patients in good general condition who have had the disease between 4 and 10 years. They also have observed 3 other cases, never treated by irradiation, showing between 10 and 30,000 leucocytes per cubic millimeter, over 75 per cent of the leucocytes being lymphocytes for 11, 15, and 22 years respectively.

Schreiner and Mattick (1924) reviewed the treatment of 16 cases

of lymphatic and 9 cases of myelogenous leukemia. Their remarks on one of their cases of acute leukemia are interesting. They note an immediate response to radiation. The patient was apparently restored to health from a moribund state in 19 days. A week later, symptoms recurred and the patient died. They agree with Niedhardt (1923-1924) who says, "There are not yet any stable therapeutic measures for treatment of acute leukemia. Yet it seems under prevalent conditions that it will be best to expect further results from roentgen ray treatment and to pay special attention to proper dosage."

Dreyfuss (1922) says, "The fairly good success attained in myelogenous leukemia stands out in contrast to the inferior results in the lymphatic type." These observations are in accord with those from other clinics. Brandt (1923) reported 14 cases of chronic leukemia, only one of which survived over 30 months. He says, "The roentgen ray does not cure leukemia but it improves the general condition, restores the earning capacity and has a favorable action on the erythrocytes."

F. C. Wood (1922) is of the opinion that while some cases of lymphatic leukemia do well under irradiation they do not respond so easily and rapidly as cases of myelogenous leukemia. The prognosis in children was not so good as in adults. Although the blood count was brought to normal in some adult patients, the disease was unchecked and progressed rapidly to a fatal end. No conclusion as to the probable course of the disease could be based on the initial blood count. He found that blood transfusion was often helpful, that irradiation of the spleen was more effective than irradiation of the long bones in myeloid leukemia, and that the roentgen ray sometimes brought back to usefulness patients who were in an extremely bad condition.

McAlpin and Sanger (1924) report the results of x-ray treatment of 16 cases of leukemia. Basal metabolism fell with the white cell curve and rose with it in a parallel manner. The count often continued to go down after treatment.

Soiland (1925b) reported a study of 51 cases of leukemia, 42 of Hodgkin's disease and 30 of lympho-sarcoma. He stated that Hodgkin's disease and lympho-sarcoma responded best to irradiation. Soiland gave to every case of Hodgkin's disease deep therapy over the site of the abdominal nodes, whether enlarged or not. He advocates the use of radium in conjunction with x-rays.

Minot and Isaacs (1926) reported the results of an analysis of 477 cases of lymphoblastoma, which included aleukemic leukemia, lympho-sarcoma and Hodgkin's disease. A separation of aleukemic lymphoma from the group would have been of additional interest to the reviewer. Reports of series of cases of aleukemic lymphoma are very scanty in medical literature.

Of the group of 477 cases above mentioned, Minot and Isaacs stated that comparisons between the lengths of the course of disease in irradiated and non-irradiated patients did not indicate that irradiation significantly affected the duration of lympho-blastoma. It seemed to do so in selected cases. The chances that the course would be prolonged appears to be relatively great for those first irradiated when their disease was in an early stage. But they warn against the possible fallacy of a general conclusion in this regard, since the duration of any such case could be paralleled by one given no special form of therapy. On the other hand, they are certain that irradiation is of great value in alleviating symptoms, decreasing the size of lesions, and in improving the efficiency of the patient. Thorough surgical excision early in the course of the disease, followed by irradiation, seemed to influence beneficially some cases of lymphoblastoma.

As to the duration of lymphoblastoma, it was noted that the average for 401 deceased patients was 2.76 years. Minot and Isaacs, in the interpretation of their statistics of both chronic lymphatic leukemia and lymphoblastoma, stress the fact that in these diseases, as in other chronic conditions, the duration is so variable in the individual patient, whether treated or untreated, that misleading conclusions may be drawn. The author of the review considers the questions as to whether irradiation prolongs the life of an average patient suffering from either chronic lymphatic leukemia or lymphoblastoma as unsettled.

#### ADDENDUM

##### *The technique of irradiation*

Part one under this section is unpublished data. It is presented therefore as addendum, since it cannot be called a review and so does not fall under the title of the paper. The remaining parts of the



section consist of a review of recently reported technique of irradiation of the leukemias and the lymphomata.

*1. Irradiation technique for the leukemias used by Dr Henry K Pancoast and Dr Eugene Pendergrass of the Hospital of the University of Pennsylvania*

Through the courtesy of Dr Pancoast and Dr Pendergrass I was allowed to compile the following summary of their technique, partly from their technique book and partly from personal communication. The reader is referred to the articles published by Dr Pancoast (Stengel and Pancoast, 1908, Pancoast, 1911 and 1917) as a background for the technique used at present in their clinic

*a. Myelogenous leukemia* For practical purposes this disease is treated as a malignant affection of the blood. The primary source of the malignancy, the bone marrow, is irradiated, as well as the places where the disease is metastasized—the spleen, the lymph nodes, the mediastinum, the liver, etc., as the enlargements occur. The body of the patient is divided into a number of sections as shown in figures 1 and 2. These sections are irradiated, usually in regular sequence with less than an erythema dose. When beginning the irradiation Pancoast and Pendergrass give one-third of an erythema dose daily for a week until it is determined whether the patient will have a reaction. The importance of the mild trial doses in the first days of treatment should be emphasized. The writer has known of several severe and harmful reactions in those cases in which irradiation was begun too vigorously, and many are reported in the literature. If the patient gives no reaction two-thirds of an erythema dose is given daily.

The factors used at this clinic are skin target distance 18 inches, a filter of 5 mm of aluminum, portal approximately 12 inches. One-third of an erythema dose is given over Portal 1 for three consecutive days. Portal 2 is then treated with one-third of an erythema dose for three consecutive days. If at this point the patient has no reaction, Portals 3 and 4 are treated, with one-third of an erythema dose over each portal for three consecutive days. Portals 5 and 6 are then treated as are Portals 3 and 4. Then Portals 7 and 8 are given the same treatment as Portals 5 and 6. This treatment takes approximately three weeks. Blood counts are taken once a week. If the

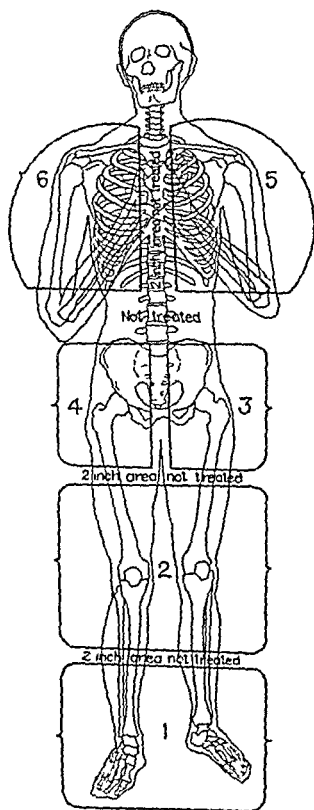


FIG 1

FIG 1 Portals of entry in sequence, anterior aspect, in the treatment of leukemia (Pancoast and Pendergrass)

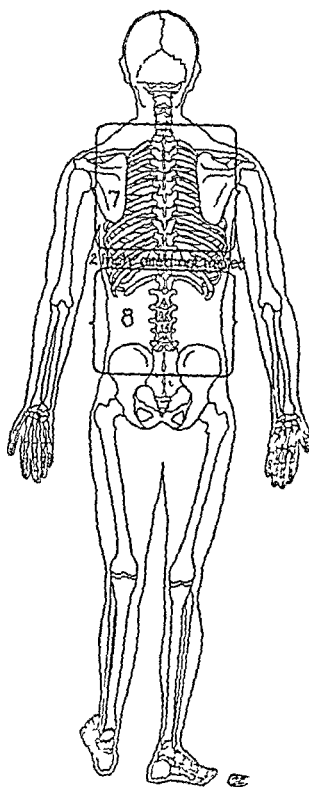


FIG 2

FIG 2 Portals of entry in sequence, posterior aspect, in the treatment of leukemia (Pancoast and Pendergrass)

two series are given over the bones the spleen is treated. It is divided into 4-inch squares and two-thirds of an erythema dose is applied to a given area each day. Complete blood counts are still taken once a week. If, after irradiation of the spleen, the blood count is still elevated the bones are treated again, provided 21 days have intervened since Portal 1 was irradiated. The treatment is continued until all of the myelocytes have disappeared, even if it causes the blood count to fall as low as 4000 white blood cells per cu mm.

In preparing a given area one fixed point for taking measurements on each leg is the external malleolus, and all descriptions of areas are taken from this point, e g Portal 1 extends from 6 inches above each external malleolus and includes both feet, Portal 2 extends from 8 inches above each external malleolus to 20 inches above the external malleolus including both knees, etc. In arriving at a given area Pancoast and Pendergrass allow 2 inches between each area to prevent overlapping, the adjacent area or portal being protected by  $\frac{3}{8}$  inch of lead and the other parts of the body by lead rubber.

The number of areas over the spleen depends on its size. Irradiation should start on the lower edge of the spleen because when shrinking occurs it is hard to tell what part of the spleen has already been irradiated. When the white blood count becomes low, daily blood counts should be made and the patient carefully observed. In cases which have become resistant to the usual technique, Pancoast and Pendergrass find that a change to deep therapy (shorter wave length radiation) again causes the desired improvement, and, similarly, after this method begins to fail, radium application will give further benefit. They emphasize that in treatment over the bones the rays are directed toward the ends of the bones rather than the shafts, because most of the red bone marrow is located in the ends of the bones and the shafts are comparatively poor in red marrow. This is a point well taken, for it has been found in reviewing technique that some outline their portals of irradiation over the shafts of the bones rather than the extremities.

*b. Lymphatic leukemia* In lymphatic leukemia they direct treatment toward irradiation of the palpable glandular areas and the retroperitoneal glands which cannot be felt. Blood counts are taken daily. The patient receives treatment over one area each day, the dosage

being one-third of an erythema dose. If there is not too much effect on the polymorphonuclear leucocytes after the patient has been treated one week, the areas are increased to two a day. Usually the glands decrease in size but the enlargement does not entirely disappear. If they do not decrease in size and there is no coincident drop of polymorphonuclear leucocytes the dosage is increased to two-thirds of an erythema dose. As soon as the polymorphonuclears begin to drop in number, treatment is discontinued and transfusion of blood is given. The entire procedure is an attempt to get the maximum effect on the glandular areas and the blood count without lowering the patient's resistance. In patients in good general condition who have isolated glandular enlargements with satisfactory blood counts the treatment is often varied so that the isolated areas are treated as indicated.

The factors of an erythema dose are

- 1  $9\frac{1}{2}$  inch distance
- 2 Filter 5 mm aluminum
- 3 Voltage 120,000
- 4 Milliampères 5
- 5 Time 11 minutes
- 6 Broad focus Coolidge tube

In lymphatic leukemia also, Pancoast and Pendergrass sometimes advise high voltage therapy or radium when the ordinary technique gives no results. In daily blood counts they keep special watch on the polymorphonuclear leucocytes. If the polymorphonuclear cells drop, they advise blood transfusion. Transfusion has seemed to them to cause a stimulative action on the bone marrow, increasing the polymorphonuclears and thereby the patient's resistance. They consider a continued fall in the red blood cells a bad sign, and recommend transfusion and interruption of the x-ray treatments for a period.

*c. Aleukemic lymphoma* This unusual type of general glandular enlargement shows the appearances of the glandular enlargement seen in leukemia but there are no blood manifestations like those of leukemia. Pancoast and Pendergrass advise extreme care in treating by irradiation and believe that one should never undertake such therapy until every other method has failed. The technique is very much like that for myelogenous leukemia. However, very much smaller doses,  $\frac{1}{16}$

to  $\frac{1}{8}$  of an erythema dose, are used. Blood counts should be made before each treatment and 24 hours after treatment. Only two areas are irradiated during a week. The indication for discontinuing treatment is the rapid fall of the white blood cells, particularly the polymorphonuclear leucocytes.

*2 Radium technique in use at the Mayo Clinic, Rochester,  
Minnesota*

The reader is referred to the article by Bowing (1923) for exact technical details. At the time of publication, radium had been used in the Mayo clinic in the treatment of about 60 cases. Bowing considers the methods described as safe and conservative. A tube containing 50 mgm of radium element or one of 50 millicuries of the emanation are thought to be equally effective. One or two tubes are used in a single application. Exact details of the filters used are given in the article. A photostat copy of the areas irradiated is appended. See figures 3 and 4. He considers the superficial glandular enlargements as the most characteristic tumors in lymphatic leukemia. Radium is applied for not more than 24 hours at one time, the usual duration of each exposure being three hours. The areas treated are as a rule two each in the right and in the left cervical region, one in each axillary region, and one in each inguinal region, thus making a total of eight areas of irradiation. If, however, the spleen is enlarged, one application only is made to each cervical region and two areas over the spleen are treated, a total of eight. The aim is to irradiate the bulk of each tumor. The usual interval between treatments is seven days. Radium is reapplied if the blood examination on the fifth or sixth day following the last exposure is found to be satisfactory. He states that the number of treatments in the one series varies from two to four, that the time interval between the series varies from six to eight weeks, and that the number of subsequent series depends upon the response and its duration. The patient is up and about between treatments but stays in bed during the exposure. To prevent irradiation of healthy parts he is cautioned to incline his head towards the opposite side when the applicator is in the cervical region, to keep the arm extended when it is in the axillary region, and not to flex the leg on the body when it is in the inguinal space. Bowing notes the in-

interesting observation that reduction in the size of distant glandular masses not irradiated occurs as soon as the irradiated tumors begin to

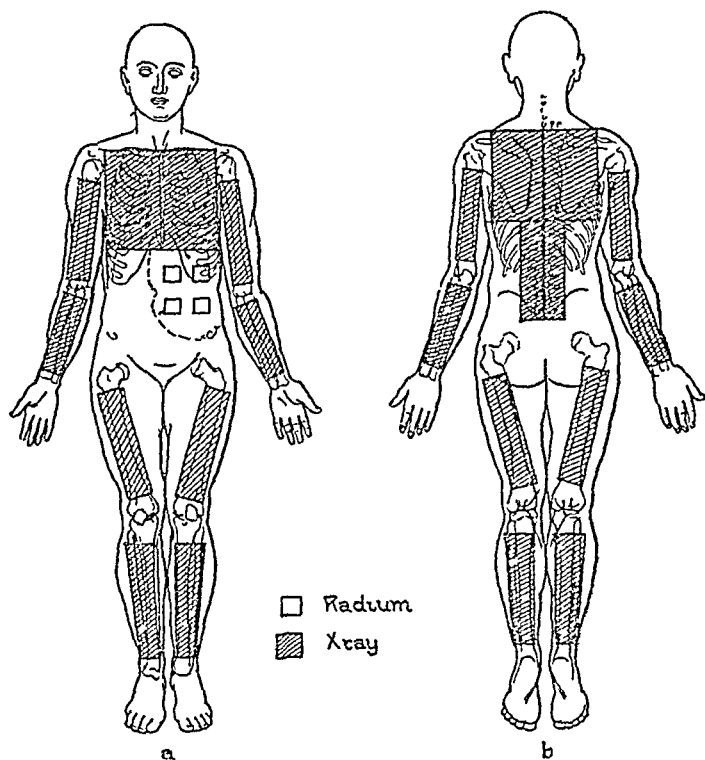


FIG 3 a, in chronic myelocytic leukemia the bones are exposed to X rays. The rectangular spaces filled in with fine lines indicate the size, location, and number of ports of entry. b, the splenic enlargement is indicated by the broken line and the small squares show the location of the radium applicator. The number of areas vary from four to six, depending on the size of the spleen. (From Bowling, 1923.)

reduce. Pendergrass (personal communication) commonly sees the same phenomena in cases under treatment. The two most important

items in determining the amount of treatment are the blood count and the general condition of the patient. The same factors largely decide the time for the next series of treatments

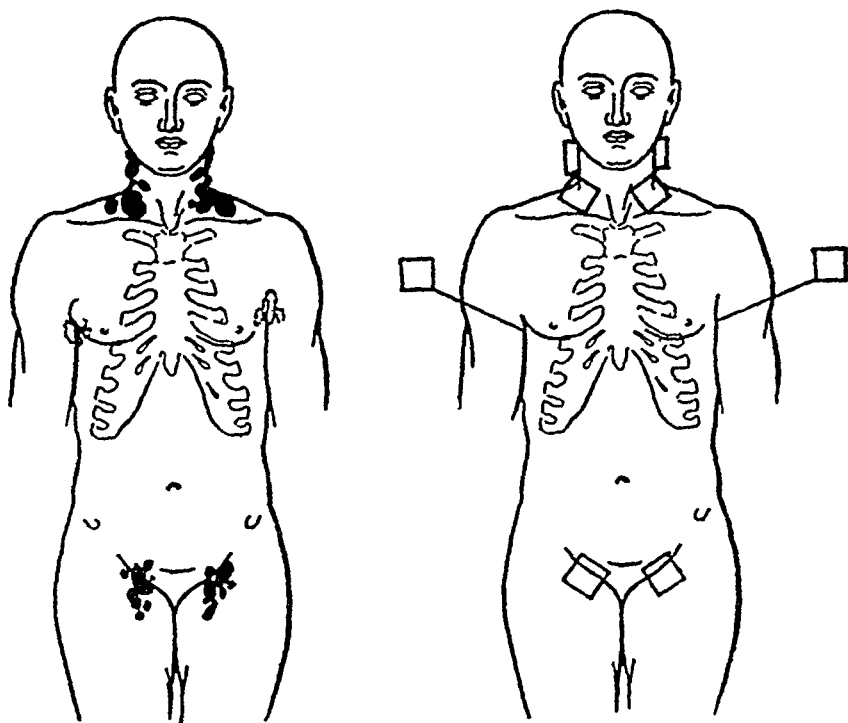


FIG. 4 The superficial glandular masses occurring in the chronic lymphatic leukemia are represented by the solid black areas and the dotted areas in the right and left axilla. The small squares show the number and location of the radium applicator. One applicator is applied at a time and changed as recommended. (From Bowing, 1923)

### 3. *Technique of irradiation for leukemia, from the College of Physicians and Surgeons, Columbia University, and the Presbyterian Hospital, New York*

The reader is referred to the article by McAlpin and Sanger (1924) for details of dosage, filters used, duration of exposures, etc. They consider it wise to reduce the treatment when the leucocyte count continues to go down. They believe that the effect of irradiation is cumulative. Irradiation is stopped for a week when a count of 50,000 leucocytes is reached after a steady fall from about 200,000. This is an arbitrary figure and there is no infallible rule as to how low the count should be. A leucocyte count should always be made before

treatment They question whether further reduction should be attempted after a count of 20,000 is reached They believe that patients do well with a count of 10,000 or lower but think that these figures should be attained only after several months of treatment By irradiation at intervals of four to six weeks the patient can often be kept in good condition and free from a recurrence As recommended by others, McAlpin and Sanger emphasize careful study of the red blood cells as a guide to the patient's condition They mention briefly two cases apparently injured by irradiation In the one the red blood cells fell to a count of a million and the hemoglobin to 20 per cent some time after irradiation had been stopped Thus they thought due to the cumulative effect of the treatment Improvement occurred after blood transfusions Curiously enough the patient lost all signs of her disease and seemed to be perfectly well when last seen about two years later

The other patient, a young man with lymphoid leukemia, was treated over the much enlarged nodes of the neck and axillae These masses practically disappeared The leucocytes fell from over 100,000 to under 10,000 He seemed perfectly well and did not return for treatment for over a year At that time his leucocytes were 112,000 and the lymphoid masses were again large He was given 3 treatments in 10 days with a drop in the leucocytes to 6,000 Two weeks later he was readmitted with the symptoms of thrombocytopenic purpura, and a blood platelet count of 10,000 He died 8 days after admission The life of a blood platelet has been thought to be about 10 days Patients who have received such an overdosage of rays do not begin to bleed, as a rule, until this interval has passed and the new crop of platelets which should be thrown into the blood stream is lacking because of damage to the bone marrow

*Technique of irradiation in Hodgkin's disease, from the Howard A Kelly Hospital, Baltimore*

The technique of irradiation both by radium and the x-ray in Hodgkin's disease has been fully described by Burnam (1926) The reader is referred to his article for details of dosage, filters, etc He calls attention to the variable and wide susceptibility to radium of patients who have Hodgkin's disease Cellular Hodgkin's responds



more rapidly than the sclerotic type Burnam begins with small dosage and proceeds with care in increasing it The localized type of disease may be treated more vigorously than the widespread type Only the actual determinable sites of the disease are irradiated as a rule If, however, the patient's symptoms do not improve after irradiation of evident masses, the deep abdominal glands are treated The bones are not irradiated He says that it might be helpful to irradiate at intervals patients apparently well in an effort to prevent recurrence He believes that a sufficient amount of radium is essential Probably 500 mgm is a minimum when mediastinal and abdominal treatments are given

The reader is referred for further details of the treatment of lymphomata by radium to the articles by Ordway (1916, 1917), Ordway and Gorham (1920), Peabody (1917), Levin (1917, 1919, 1922), Rénon and Degrais (1921), Rénon, Degrais and Tournemelle (1914), Oppenheimer (1921), Stern (1922), Gulland (1921), Henriques and Wenville (1922-23), Béclère and Béclère (1913-14), Elliot (1918), and Whitcher (1922).

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## INTRODUCTION

### DEFINITION OF EPILEPSY

Epilepsy in the Greek means "I seize," or "seizure." Most authors of the present accept the literal meaning of the word and think of "epilepsy" as "seizure" i.e., as a symptom rather than as a disease entity. For the present discussion, we define it as a syndrome characterized by the sudden appearance of paroxysms, of which convulsive movements or loss of consciousness or both, are a principal element. Many writers have segregated patients who present no significant abnormality on physical examination, and whose seizures, therefore, are presumably due to an inherent tendency to react with convulsions,

into a group labeled "Essential" or "Idiopathic " Because it seems probable that all patients having seizures from whatever apparent cause possess this susceptibility to seizures in some degree, and because we have no means of determining whether it forms 10 or 90 per cent of the total influences making for seizures, the clinical use of such a term as "essential" only obscures the issue, making discovery of the underlying cause or causes more difficult. Some disturbance of the brain exists in all cases in which seizures occur. *Epilepsia sine materia* is a dead expression (Laignel-Lavastine and Voisin, 1925). It would, perhaps, be better to drop the term "epilepsy" and speak simply of "paroxysmal disorders" or of "the convulsive states ". Because of usage and for the sake of brevity, we shall use the term "epilepsy ". It will be evident, however, that many of the authors, whose observations we shall quote, regard epilepsy as a disease entity.

#### CONDITIONS SOMETIMES ASSOCIATED WITH SEIZURES

First in importance stand diseases in which there is structural derangement of the central nervous system, a list of which is given in the section dealing with pathology of the nervous tissue. Other disorders are hysteria, conditions associated with the blood and circulation, as syncope, Stokes Adams disease, paroxysmal tachycardia, polycythemia and sudden anemia, and many other conditions of more or less recognized etiology, eclampsia, tetany, fevers and many irritative conditions in childhood.

#### SCOPE OF PAPER

Affliction with seizures is an ancient and a widespread condition. In the United States, if we may accept for the whole population the incidence among drafted men, something less than 500,000 persons are subject to "epilepsy,"—Davenport (1923). The lot of these persons is a difficult one. The care of those who need it constitutes a heavy charge on families or communities, their treatment is oftentimes no more rational than was given in the dark ages and beyond.

The investigation of epilepsy has not kept pace with that of many other medical conditions. As a preliminary to a study of the question, it is essential that there should be a survey of our present knowledge

We should be in possession of all the facts, positive and negative, concerning the bodies and minds of persons subject to convulsions. It is evident that in any such survey the attempt must be made to segregate fact from fancy and objective description from speculation. Explanations of unseen things there must be, but such deductions must, if possible, be based on evidence

Under the heading "Epilepsy" the index catalogue of the Surgeon General's office (1925) contains approximately 3000 titles. Gruhle (1923) in his uncritical review of the literature from 1910 to 1920, mentions 1000 articles. It is manifestly impossible to discuss here the whole subject of epilepsy. We shall confine ourselves to the presentation of evidence which may throw light on the mechanism involved in seizures, and on the cause and treatment. As a further limitation in presenting evidence from clinical sources, we shall be concerned largely with patients whose seizures are of unknown origin

Authoritative discussions of the subject of classification as well as of certain aspects which are outside the scope of this paper will be found in books and in articles by the following authors: Campbell (1917), Kraepelin (1919), Redlich (1919), Frisch (1921), and Wilson (1926).

## NEUROLOGICAL CONSIDERATIONS

### LOCALIZATION THEORIES

There has always been much speculation as to the locus of origin of the epileptic attack. The early stimulation work of Fritsch and Hitzig (1870) and others, turned the attention of investigators to the motor area of the cerebral cortex, but with further analysis the symptomatology seemed too complex to be explainable on the grounds of simple cortical stimulation. Fischer and Leyser (1924) divide the investigators into two schools: those who hold to a purely cortical origin for the convulsions, and those who believe that the seat of the clonic phase is in the cortex and of the tonic phase in the basal ganglia. Dandy (1927b) on the basis of 6 experiments on dogs believes that clonic convulsions can originate only in the motor cortex. This does not agree with the observations of Uyematsu and Cobb (1922) or of Foerster (1926) who have seen convulsions in the hind limbs of spinal

animals Ziehen (1890) believed in the cortical origin of clonic fits, and the subcortical origin of tonic phenomena, Rothmann (1912), Binswanger (1922) and others agree with this schematization Muskens (1926) always sees myoclonus as the basis of attacks Krisch (1924) on the other hand, sees in the epileptic motor attack a stormy and sudden disturbance of the same tract systems that are more chronically disturbed in dystonia In other words he looks on epilepsy as an extra-pyramidal syndrome Again, there are those who believe that epileptic seizures originate in the medulla, in fact almost every division of the brain has at some time been held responsible

A review of the literature and clinical observation, however, give one the impression that all this localizing is too schematic Certain patients having repeated, stereotyped fits do appear to have a focal origin for their attacks But, as we point out later, the observation of a convulsion is a most difficult thing and if an observer is interested in "medullary symptoms" he cannot at the same time closely watch the "cortical" and "striatal" phenomena Thus the descriptions of attacks may be biased, and one phase of the symptomatology emphasized at the expense of another On the whole, one is inclined to agree with Fischer and Leyser (1924) that too much anatomical schematization is unjustified Fits can be set off by stimulation, or by disturbances such as anemia, of various parts of the central nervous system, and convulsions may occur after removal of the cortex and even in the isolated cord Thus one must return to the more general conceptions of etiology and consider a focal lesion as the cause only when it is obviously indicated by the symptomatology and pathology

#### NEUROLOGICAL MECHANISMS OF CONVULSIONS

##### *The irritation theory*

Much has been written on the physiology of convulsions Experimental stimulation of the motor cortex gave impetus to the idea that convulsions always originate from irritation of the cortex Since it is demonstrable that irritation of the motor area can cause focal convulsions, it is reasonable to suppose that irritation of other areas, by spreading to the motor area, can cause an overwhelming motor

discharge externalized as a general convulsion. This conception still has many adherents and is supported by both experimental and clinical evidence. In the first place Sherrington (1925) and others have elicited both focal and general convulsions by electrical stimulation of the motor cortex of animals. A weak stimulus causes a normal movement appropriate to the cortical area stimulated. Repeated stimuli cause focal convulsion of the affected muscle group, stronger stimulation causes first focal and then generalized convulsion. The question arises—is this convulsive movement due to irritation; i e, to excessive stimulation, or is it due to temporary functional destruction of the motor nerve cells? C. and O. Vogt (1922) have shown that electrical stimulation of the cortex causes marked chromatolysis in the nerve cells, and this helps to support the theory that excessive stimulation may act by inhibiting motor discharge rather than by causing excessive discharge.

In order to comprehend the cerebral efferent mechanism, it is important to realize that the motor cortex is "motor" only in a broad sense. It is rather *sensori-motor* as indicated by the experiments of Dusser de Barenne (1924) and others, for upon this region of the cortex converge many association pathways from the various sensory receiving stations. These set up appropriate efferent responses. Thus the motor area is really a terminal nodal point from which highly integrated influences finally travel to the ventral horn cells of the cord. The only way in which we can express ourselves is by muscular contraction, so the extraordinarily complex associative mechanism of the cerebral cortex must have an outlet to the muscular mechanism. The first and most complex stage of this efferent system is the motor cortex which receives and organizes the stimuli, thus initiating specialized voluntary motion. "Voluntary" here means "most highly integrated," that is to say—long delayed stimuli stored as memory, as training or as experience may condition the reflex response to any immediate stimulus. Elaborate reflexes are coordinated at this level, but efferent discharges are transformed into motor activity only at the lowest level where peripheral neuron stimulates muscle. Before this takes place other lower and more primitive centers add their influence to make the cortical influences effective. Schematically it may be said that the postural and tonic centers of the basal ganglia,

mid-brain and medulla give the basis from which to start voluntary movement, postural influences hold the body erect, appropriately placed in respect to the center of gravity, allowing such motor activity as walking without waste of conscious effort. The cerebellum coordinates these two—the voluntary from above and automatic from below. It takes the body as it finds it at any instant and interprets in an effective and orderly way the orders from the cortical headquarters. In Babinski's (1900) phrase—the cerebellum synergizes. Lastly the ventral horn cells of the cord deliver to the muscles the coordinated impulses. The complications of this process are so great as to be well nigh incomprehensible. A simple reflex, such as that of stepping, may involve an intricate maze of connecting and cross connecting neurons (Sherrington 1925). But for purposes of exposition one may divide the central nervous system into five motor levels (see fig 1) (1) cortical ("voluntary"), (2) basal (automatic associative, postural), (3) cerebellar (synergic), (4) spinal (simple reflex), and (5) neuromuscular (the final common path along which all impulses from above must travel to reach the effector organ, the muscle).

To return then to the electrically stimulated cortex. What happens? Does this highest motor level cause a convulsion because it is overstimulated, or because it is thrown out of action altogether and the lower centers are freed to act? The former hypothesis is that of Jackson (1873). Stimulation by pathological irritation of a sensory zone causes an aura, the discharge spreads with increasing force to the motor area and the convulsion begins. Gowers (1881) ably supported this discharge theory by clinical evidence. His description of a typical attack is still a classic. It is quoted verbatim.

*"Major fits* At the onset of the severe fit the spasm is tonic in character, rigid violent muscular contraction, fixing the limbs in irregular positions. There is usually deviation of the eyes and rotation of the head towards one side, and this rotation may involve the whole body, and sometimes cause the patient to turn round, even two or three times. The tonic spasm involves the muscles of the chest and abdomen. The features are distorted, the face, usually at first pale, becomes suffused and then livid, as the chest is fixed and respiratory



movements are arrested. The eyes are open or closed, the conjunctiva is insensitive, the pupils dilate widely as cyanosis comes on. As

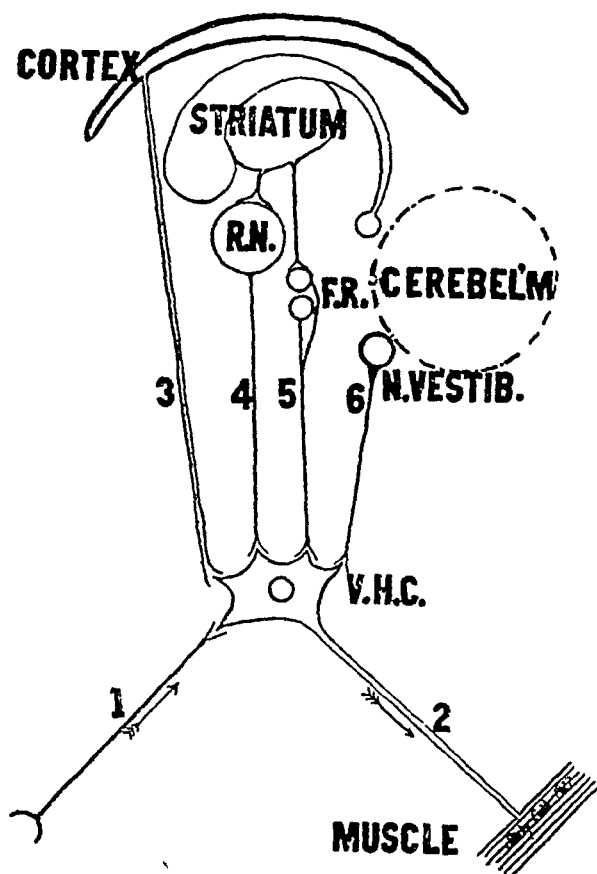


FIG 1 DIAGRAM OF THE VARIOUS NEURON LEVELS WHICH PLAY UPON THE VENTRAL HORN CELL (V. H. C.) AND CAUSE CONTRACTION IN THE MUSCLE VIA THE "FINAL COMMON PATH" (2)

Afferent impulses may come in from a sense organ and directly effect the ventral horn cell by way of the simple reflex arc (1). The cortico-spinal tract (3) sends down highly integrated impulse-complexes which take precedence over the simpler ones from the nucleus ruber (R. N.) the formatio reticularis (F. R.) and the nucleus vestibularis (N. Vestib.), which traverse, respectively, the rubro-spinal tract (4) the reticulo-spinal tract (5) and the vestibulo-spinal tract (6). But it is the combination of pyramidal (3), extra-pyramidal (4 and 5), vestibular (6) and spinal (1) impulses, all harmoniously playing on the motor cell that causes normal synergic movement.

the spasm continues, it commonly changes in its relative intensity in different parts, so that slight changes in the position of the strained limbs occur. Presently, when the cyanosis has become intense, the

fixed tetanic contractions of the muscles can be felt to be vibratory, and the vibrations increase to slight visible remissions. As these remissions become deeper, the muscular contractions become more shocklike in character, and the stage of clonic spasm is reached, in which the limbs, head, face, jaw, and trunk are jerked with violence. In the resulting movement of the chest, air is expelled from the thorax, and bloody saliva is frothed out between the lips. The air entering the lungs is at first insufficient to lessen the lividity, and the patient may seem to be at the point of death. But as the intervals between the shocks of spasm lengthen, and the remissions become greater, more breath enters the chest, and the lividity lessens. In becoming less frequent the muscular contractions do not become less strong, and the last jerk is often as violent as those which have preceded it. At last the spasm is at an end, and the patient lies senseless and prostrate, and usually sleeps heavily for a time, and then can be roused. Urine frequently, and faeces occasionally, are passed in the fit."

This paragraph vividly portrays the main events of a seizure. Of special interest is Gowers' physiological understanding of "tonic" spasm as really "tetanic," becoming "clonic" through discontinuity rather than by any essential change in level of innervation. Physiological proof of the correctness of this view was brought forward 44 years later by Cobb (1924) whose electromyographic studies of experimental convulsions show that both the sustained steady contractions of the "tonic phase" and the interrupted recurrent contractions of the "clonic" phase are tetanic, both being accompanied by rapidly alternating action-currents in the affected muscles.

This description, and the elaboration of it in the following pages of Gowers' book, as well as one's own clinical experience, do not corroborate the view that attacks follow a regular sequence of events affecting first the higher and then the lower centers. Gowers describes various postures of arms, hands, legs and trunk, sometimes flexion, sometimes extension. Clinical observation shows that the most common tetanic posture is extension of legs and trunk with flexion of arms and carpedal position of the hands, this cannot be said, however, to be a rule. One feels that those authors are too schematic who describe the spread of the convulsions down along the neuraxis,

affecting each level in turn—cortical, basal, bulbar and spinal. Accurate observation of a convulsion is difficult. The recent slow moving picture technique has been most useful. Of special interest are the pictures shown by Stenvers (1925) demonstrating that the movements in a convulsion are not meaningless myoclonic phenomena, but are integrated movements. This observation corroborates once more the observations of Gowers (1881, p. 72) who in speaking of the muscles involved in a convulsion says "The association is of the movements not necessarily of the muscles." All this points towards cortical discharge as the source of the convulsion for it is the cortex that innervates *movements* as opposed to the segmental innervation of muscles in the bulb and cord. Furthermore, there are the wellknown cases (one of them quoted by Gowers (1881)) in which hemiplegia occurring in a chronic epileptic patient results in cessation of the fits on the paralyzed side. The supposition is that a lesion in the internal capsule cuts off the cortico-spinal path and thus blocks the downward spread of cortical impulses on that side.

Foerster (1926) opens his discussion of the pathophysiology of epilepsy by saying:

"The epileptic attack is nothing more than a special symptom, more exactly a syndrome, since it is a very complex phenomenon. It is a special form of reaction of the central nervous system—a reaction to stimulation. It is an irritation syndrome, not a release phenomenon as has been long held by different authors, even at present by many. Two main arguments speak against the theory that the epileptic convulsive attack results from the release of individual action of nerve centers because of a sudden paralysis of higher inhibitory mechanisms. In the first place, after the sudden removal of the inhibitory mechanisms in man, one does not see immediately the positive signs of release. In the vast majority of cases these signs develop after a distinct interval during which there is a decrease of the activity of the lower, released centers as well as of the higher inhibiting centers. Then the release phenomena appear little by little, never cataclysmically as in the epileptic fit. It is not meant that some release symptoms cannot appear in such a complex syndrome as that of the convulsive attack, but the greater

part of the phenomena cannot be explained by removal of inhibition. The second argument is that the Faradic current (the very agent by which we can most easily and surely elicit convulsions) is an exquisite means of stimulation, the very prototype of active excitation. Thus the fit does not resemble the horse suddenly freed from control of bit and spur by the breaking of the bridle, but rather the horse, which until now is undisturbed, suddenly rears because the spurs are jabbed into his flanks."

### *The release theory*

Hughlings Jackson (1873) first suggested that convulsions might be a release phenomenon. Recently Sargent (1921), Rosett (1923), Hartenberg (1926) and others have supported the theory that epilepsy is a release phenomenon arising from *inhibition* of cerebral centers rather than from their excitation. Within the last year Martin (1926) has summarized this point of view. He describes a typical fit, notes the various phenomena that might be considered inhibitory in origin, and says

"Thus in analyzing the full epileptic fit I have not found any unequivocal evidence of cortical stimulation, but, on the contrary, in the prodromal symptoms, in the unconsciousness, and in the presence of an extensor plantar response at the end of the clonic stage I see indications of cortical inhibition, the movements of the clonic stage may be explained either by cortical or by brain-stem and spinal action, but the latter explanation is much more in accordance with the other elements of the fit."

Before we can discuss the theory that epileptic convulsions are release phenomena, arising when the higher centers lose control, we should secure a clear understanding of what this "control" really is. Fulton (1926) in his last chapter discusses in a most illuminating way the nature of higher control and offers two diagrams to illustrate the salient points brought out in recent investigations. In the first place, the conception of the "final common path" of Sherrington (1906) is essential. Sense organs are continuously sending in stimuli of various sorts, each has its own path and carries its own impulses for central integration. From these integrating centers several path-



many authors have since elaborated his scheme (see fig 1) It is obvious that all impulses reaching the cord must be coordinated by some mechanism in order that the muscles shall respond in an orderly and effective way Just such a mechanism is given us by Fulton (1926) whose figure 204 is here reproduced (fig 2) Physiologically such a diagram is well sustained, and there is also a certain amount of anatomical evidence upholding Fulton's postulates

A study of these two figures shows that higher control of the final common path must come from a delicate balancing of excitatory and inhibitory stimuli In Fulton's own words

"It may be taken, therefore, as an adequate generalization that the full dominance of the highest levels of the brain is made possible through power to excite and to inhibit activity of lower centers "

Figure 1 shows how cortico-spinal, rubro-spinal, reticulo-spinal and vestibulo-spinal influences<sup>1</sup> all impinge on the final common path For simplicity let us discuss the cortico-spinal and vestibulo-spinal influences only, as typifying the usual conception of "voluntary" and of "tonic" impulses We have thus three main sources of energy (1) From the afferent paths, which reach the dorsal roots and cross to the ventral horn cells, these may be conveniently divided into those subserving the exteroceptors—such as touch and pain (nociceptive) and those subserving proprioceptors—such as muscle and joint sense organs (2) From the afferent paths which reach the vestibular nuclei directly and via the dorsal longitudinal fasciculi (3) From the vast complex of association paths, originating in cortical receiving stations and converging on the pre-central area of the cortex, these set up impulses in the cortico-spinal path Both inhibitory and excitatory influences can come over any of these routes Figure 2 shows how myotatic reflexes can give tonic responses at the spinal level, and how they can be suppressed by nociceptive stimuli coming in from the exteroceptors of the skin A similar process, but in enormous complexity, evidently goes on at all the higher levels Essential to the whole process of integration is the fact that at the spinal level there is a blocking mechanism which may prevent *immediate* reflex action,

<sup>1</sup> Recent work by Papez (1926) and Morgan (1927) shows that the rubro spinal path is less important, while the vestibulo spinal and the reticulo-spinal paths are more important, for motor integration

and which may divert impulses up the cord to higher centers. This mechanism Fulton (1926) aptly calls "long-circuiting," and says:

"It is obvious that the process of long-circuiting of impulses up the cord is of fundamental importance for the integrative processes occurring in the higher centers. It would appear, moreover, that so long as a given controlling higher center is present, the majority of afferent impulses are long-circuited in this way. When, however, the higher centers are cut away, the majority of impulses pursue the phylogenetically older paths across the cord."

This is a conception with many interesting implications relative to explosive cerebral phenomena, such as fits. *Long-circuiting* in itself leads to delayed action, gives higher integration and causes stimulation of many more association paths than does direct spinal reflex action. This process of spread is essential for coordination. Its acme is found in the cerebral cortex where stimuli arriving at one receiving station (e.g., the visual "center") spread in innumerable directions to many other cortical areas, awakening associations, habitual responses, memories, etc. This causes a *delay in response*, clearly a most useful mental process, for while the delay lasts the spreading impulses are allowing the past experience of the individual to effect his behavior, this activity of the association paths may be the essence of "mind." Long-circuiting, though it causes delayed action and prevents impulsive behavior, is probably not true inhibition for it involves the whole complexity of cerebral activity (Cobb, 1928). The term inhibition should be saved rather for the simpler physiological processes taking place, for example in or about the ventral horn cells of the cord, as indicated in the diagrams of Fulton here reproduced, and in those of Sherrington (1925), Forbes (1922) and Lucas (1917).

The impulses descending along the cortico-spinal tract traverse the synapses associated with the ventral horn cells or their internuncial neurones. These impulses lead to excitation or inhibition according to laws as yet unknown. Impulses descend the rubro-spinal tract (see fig 1) which likewise has varied endings, and their influence may be either excitatory or inhibitory. The spinal mechanism is undoubtedly similar. The whole intricate mechanism depends upon integration and it is evident that no such simple formula as the "removal

of cortical inhibition" can explain in their entirety the varied phenomena of decerebrate rigidity. There is certainly a release of lower centers when higher centers are destroyed, but this is not a release from simple inhibition, it is release from a great complex of influences, and is different for each animal, since each species varies in the amount and type of its "long-circuiting."<sup>2</sup> For example, a decerebrate man lies with legs extended and arms partly flexed, a decerebrate cat stands with all four limbs extended, tail and head raised, a decerebrate sloth takes its claspings, pendant posture (Richter and Bartemeier, 1926) and a decerebrate frog squats with legs flexed.

With these conceptions of higher control in mind, it is interesting to consider the theory which looks upon fits as release phenomena, holding that convulsions arise not from stimulation or irritation, but from temporary suspension of the functions of each level, in sequence from above downward, this allows the lower centers to act in an uncontrolled way, and thus explosively and excessively by convulsion. Certain authors thus look on a fit as an acute temporary decerebration, and describe how suspension of cortical function may release the striatum, the mid-brain or the cerebellum to cause fits, and how these in turn being *hors de combat* allow the medulla and cord to produce their simpler and more lowly forms of fit. For example, Yakovlev (personal communication) tells of a patient who repeatedly has the following epileptic seizure: while sitting in a chair he suddenly looks blank and becomes unconscious of his surroundings, next he straightens out rigidly, falls, and goes through dystonic and athetoid movements, then clonic movements take place for a few seconds, finally stupor supervenes with involuntary micturition. This is explained as illustrating in sequence (1) decortication (absence), (2) decerebration (rigidity, athetosis, clonus), (3) isolation of bulb and cord (stupor and loss of sphincter control). Gordon (1928) describes an unique case where a boy was taken with a fit during a dictation exercise. He wrote twelve words of most interesting "jargon agra-

<sup>2</sup> "Encephalization" is essentially "long-circuiting"—the more the function is taken up by the higher centers in brain, the more impulses must be diverted up the cord by long-circuiting mechanisms. The conception of long-circuiting, delayed response and encephalization would seem, then, to be fundamental for the understanding of intelligent behavior and especially abstraction.



phia" before he fell over unconscious. Gordon believes that this illustrates the true nature of an epileptiform fit as a release from higher cortical control

Martin (1926) was quoted above as an exponent of the release theory. His paper is based on clinical observation and explains well the phenomena enumerated. But it is the exceptions that test the rule, and atypical as well as typical convulsions have to be explained. For example, he describes the common prodromal apathy as an indication of cortical inhibition, stating that it "may be taken as a general rule that epileptics will not have a fit during a period of intense mental activity or of enthusiasm." This hardly holds, for in any large series of cases some are found who have periods of elation preceding their attacks, or who have attacks in the midst of excitement or athletic activity.

In discussing the clonic movements of the legs, Martin describes them as spinal reflexes like the "walking reflexes" of a decerebrate animal. This is obviously a reasonable analogy, but one cannot agree when he states that "this reflex can only be elicited when the cortical control over spinal centers is removed." It is a daily experience with all mammals that their walking reflexes function perfectly while their cortical centers are active. One surely cannot argue that, because rhythmic progressive movements are being carried on by the legs, the cortex is inhibited. Martin proves his point that it is unnecessary to involve cortical activity to explain clonic movements, but it would appear to be equally unnecessary to involve cortical inhibition.

Another argument brought forward by this author is that exhaustion of the cortical cells cannot explain the post-convulsive appearance of Babinski's sign because of the "fact that a second and equally strong fit may occur within a few minutes." He believes that so quick a recovery of the cortical cells is unlikely. Common experiences with chloroform and nitrous oxide anesthesia, or with sleep, would seem to show that suppression of the cortical cells is quickly brought about and quickly removed. Pavlov's (1925) experiments on inhibition and the causation of sleep support the supposition that cortical inhibition may be rapidly transitory. Moreover, experiments on other organs indicate that with return of normal circulation the products of even great fatigue are quickly carried away.

Better evidence for cortical inhibition is the observation of Yakovlev (personal communication) that in some minor attacks, where fatigue of the motor cells seems an unreasonable postulate, the Babinski sign may be elicited almost at the beginning of the attack. And he adds with good reason that all we know of the sign of Babinski indicates that it is evidence of interference with the cortico-spinal tract, not stimulation of it.

Martin also explains post-epileptic automatism as an imperfect recovery from cortical inhibition, the motor functions having recovered and the psychic being still partially in abeyance. A perfectly good explanation, but perhaps not as satisfying in cases of psychic "equivalent" as a theory of excitation. For in these cases the motor functions may never be disturbed, the symptoms being entirely at the psychological level. He also refers to the uniformity of the seizure as an argument against the theory of cortical stimulation, saying "Though there are some variations the elements of the attack are the same and their sequence is the same in nearly all cases." With this statement one cannot reconcile one's clinical experience, epileptic attacks are among the most variable and bizarre of neurological phenomena. Indeed though Martin's observations may be taken as evidence for cortical inhibition, one cannot agree that he has assembled enough facts, nor by those facts put forward does one feel forced to accept his conclusions.

These schemata are helpful in explaining many phenomena, and Jackson's conception of release is one of the most valuable in neurology, but such formulations do not, in the writers' opinion, explain convulsions. Such a theory is too orderly and depends too much on the idea that the central nervous system, like a telephone exchange, is made up of reflex arcs and levels. If decerebration by sudden anaemia, emotion, shock, or inhibition causes a fit, why are not all states of unconsciousness ushered in by convulsions? We do not have a fit every night as we fall asleep. Patients with epilepsy "going under" an anesthetic only rarely have convulsions. Moreover, this theory presupposes that the "motor" area of the cortex is largely inhibitory. Fulton's theory, quoted above, indicates that both excitation and inhibition occur at all levels of integration. Cooper and Denny-Brown (1927) have recently shown this experimentally in cortical

stimulation they infer that excitatory and inhibitory units lie microscopically intermingled in the cortex and that the epileptic discharge may be one of the signs of conflict of summated excitation and inhibition. Pavlov (1927) looks on the cortex as a mosaic of excitatory and inhibitory spots. Thus the best physiological evidence argues against the possibility of either a pure excitation or pure inhibitory release

### *The short circuit theory*

There is a body of facts which points to the conclusion that any thing which reduces the complexity of the cerebral associative mechanism may lead to convulsions. Thus the simplified reflex arcs do not benefit by the delaying effect of elaboration, and allow explosive motor discharges to escape. Trauma with gliosis, wide-spread hemorrhage or inflammation, aplasia with microcephalus might have such an effect on conduction. This theory obviously is akin to that of release just discussed, for short circuiting is a kind of release. In the electrical analogy, the current avoids resistance by taking a new and shorter path, the short circuit. "Release" would in this case be symbolized by removal of the resistance coil. The main difference between the release and short circuit theories is that in release we think of removal or inhibition of a large functional unit of the central nervous system (cortex, striatum, mid-brain), whereas in the short circuit conception, any small or large portion of nerve-conduction arc may be undermined and "short circuited". This theory would explain great variation in symptomatology and perhaps the fact that there seems to be no sharp distinction between the obviously organic focal epilepsy and the "idiopathic" epilepsy. We find focal lesions causing focal convulsions, or focal convulsions spreading to become general convulsions. We may have diffuse lesions causing general convulsions or somewhat focal (though variable) convulsions. Moreover, we may have convulsions with no discoverable lesion.

The fact that Frazier and Ingham (1920) found that wounds of the parietal region caused convulsions more frequently than those of other parts of the cortex is interesting in view of Southard's theory of "epileptogenic foci"—areas in the cortex where lesions with gliosis have cut off association tracts and caused abnormally simplified reflex

arcs Over these simple arcs it is conceivable that uncontrolled discharges may pass too easily, causing epileptic phenomena In Southard's own words (1908)

"A reduction or simplification of the system through destruction of the smaller elements of the cerebral cortex procures new reflex arcs with fresh surfaces of separation which are perhaps even simpler and more automatic than the spinal arcs and synapses The peculiar features of the epileptic discharge depend upon the inertia of currents travelling in simplified arcs, and upon the lack of energy-absorbents en route The cerebral arcs normally escape automatism through a multitude of synaptic connections, under epileptic conditions the cerebral mechanism approaches in fatality the spinal mechanism "

"The phenomenon of epilepsy, in short, requires the intactness and even the normality of some well-defined route from stimulus to muscles "

"Destruction of elements at any point in the route should at first sight exclude the production of epilepsy And so, in most cases, the destruction of the afferent paths will exclude epilepsy In the afferent paths, however, the very process of destruction often constructs new and potent surfaces of stimulation which act as epileptogenic foci, and, in the cerebral synaptic tissue, the strata are so constructed that the loss of smaller, central, modifying, and inhibitory elements is effected prior to the loss of the major elements which are essential to the intactness of the great route And these major afferent elements can themselves be subject from time to time to stimulation afforded by the contractile energies of growing neuroglia Epileptogenic stimuli are applied in all cases to those elements having a forward direction, so that the reaction is in most cases, if not necessarily, a sensorimotor reaction in Hughlings Jackson's sense "

"With the onset of topographic and stratigraphic knowledge of the cerebral cortex, we shall approach more nearly to a definition of tissues suitable for the propagation of epileptic discharges So far it seems that such synaptic tissues are characterized by abnormally simplified arcs whose impulses are the more automatic through the lack of counter-currents from surrounding cells "

Although all the details of this explanation may not be acceptable, yet the similarity in thought to Fulton's conception of long-circuiting and delayed response is striking, and supports the application of these ideas to epilepsy.

Further evidence that "simplified arcs" tend to cause epileptic motor discharges is found in the feeble-minded. Here we have much epilepsy among the lower grades, and these patients have more or less simplified brains, with a characteristic lack of association fibers. Even in the moron group we find epileptics who at autopsy are shown to have reduced hemispheres. The hemisphere shown in Fig 3 has little frontal lobe development and more closely resembles the cerebral hemisphere of a chimpanzee than that of a human. The patient was feeble-minded, had had convulsions since the age of 16, and although he lived to be 60, only reached a mental age of about 9. The fact that children are so much more prone to convulsions than adults is perhaps explainable on this theory of "simple brains" and simplified reflex arcs too easily conducting abnormal motor discharges. Children's brains are not fully myelinated, complete development in this respect not taking place until the sixteenth or eighteenth year.

In summarizing this "short circuit" theory the authors are alive to the danger of theorizing on the basis of analogy. A great many explanations of the fit have been written which use the electrical analogy in a loose way speaking of "insulation of neurones," "storage of energy," and the like. Recently Alford (1926) in a plausible paper uses a hydrodynamic symbolism and speaks of "floods of nervous energy increased above the normal level." If we are to progress it is necessary to keep within our scientific limits and use data and terms based on clinical or experimental observations. A careful study of Sherrington's papers and especially of the work of his recent collaborators, Fulton, Cooper and Denny-Brown, gives one a standard of care in terminology well worth emulating. When epileptoid reactions can be accurately described in terms such as "relaxation," "contraction," "phasic" reflex" and "clonic after discharge," each of which has a demonstrable physiological basis, we can be more sure of our ground when we come to theorizing. At present even the "inhibition," even when applied to simple spinal reflexes, has not been satisfactorily explained and defined.

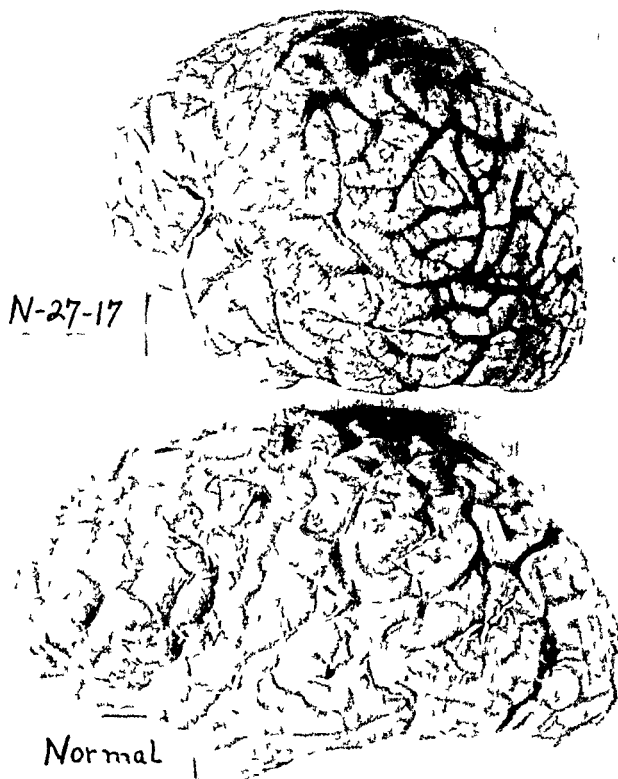


FIG 3 THE UPPER HEMI-SPHERE (CASE N-27-17) IS FROM A TIDDL MINDED EPILEPTIC

The conspicuous abnormality is the aplasia of the frontal lobes. A hemisphere of normal proportions is shown below for comparison. Lack of frontal lobes theoretically might lead to short circuiting of impulses or release of lower centers (see text)

*The explosive theory*

A spreading stimulus arising from a local irritation as described by Jackson, adequately explains the phenomena of aura and onset of convulsions, but the fall, the unconsciousness and the motor discharge are often too overwhelming, sudden and disorderly to be explained by any sequential blotting out of reflex levels. Neither does progressive irritation of one level after another give a satisfactory explanation, for the same reason. Text-book pictures of convulsions with their clonic, tonic and flaccid stages are misleading. The distinction between "clonic" and "tonic" spasm is clinical, but cannot be explained on an anatomical localization of the convulsive process. Fits are sudden, disorderly motor discharges, infinitely variable and often affecting almost simultaneously large portions of the central nervous system. To understand them it would seem more rational to look on the brain as a whole, to study it as a "physiologische Gestalt," and to see what processes affecting the brain as a unit organ of more or less homogenous cytology might be responsible for convulsive phenomena. Obviously the central nervous system has certain properties common to all its different parts. Following Kohler (1926) one might mention temperature, pressure, concentration, electrical potential, and reaction (pH). One must conceive of changes in these physical properties as affecting all centers, and all centers affecting the impulses, influencing what they shall be and, to a certain extent, where they shall go. In short, we must allow for dynamic interaction in the physical sense. Such changes effect the whole central nervous system. They argue against the conception of a blind impulse running from one center to the next, awakening reflexes as a train of gunpowder sets off a series of blasts. The evidence gained from experimental convulsions shows that many drugs can cause convulsions—absinthe, cocaine, camphor,—to enumerate only a few. These give fits somewhat similar to the seizures occurring in patients. Moreover, we have many general changes in the body which may bring on convulsions—anoxemia, alkalosis, anemia, hypoglycemia. These factors do not seem to act in any selective way on any one neuron level, but by a widespread and sudden metabolic change over a large part of the brain.

Syz (1927) using acid fuchsin as a convulsant in frogs showed that injury to any part of the central nervous system caused a change in the permeability of the whole brain and cord to this dye with a resulting increase in susceptibility to convulsions. He emphasizes the complexity of the process and suggests that stimulation might cause changes in the blood vessel walls and increase their permeability. Anaphylaxis, probably the result of primary action on capillaries, is a similar phenomenon. The explosiveness, general symptomatology and variability of seizures resemble anaphylactic reaction, and it is possible that the mechanism involved, though not identical, may have certain features in common.

### *Summary*

Search for the anatomical locus from which fits arise has occupied many investigators, but all this localizing is too schematic. Fits can be set off by disturbances in various parts of the central nervous system. The evidence does not justify calling them all "pyramidal," or "extrapyramidal," or "medullary" phenomena. Little is really known of the neurological mechanism involved in an epileptic seizure. One may discuss this mechanism by describing four theories: (1) The "Irritation" theory which arose from the electrical excitation experiments and the pathological findings in Jacksonian epilepsy. (2) The "Release" theory suggested by recent advances in physiology, e.g., our newer interpretation of decerebrate rigidity, or of locomotor reflexes. This theory holds that convulsions come, not from stimulation, but from a temporary suspension of function of the higher centers which allows the lower centers to discharge explosively. (3) The "Short-circuit" theory is obviously allied to the release idea, but is more local. A cortical lesion (for example) is considered capable of interrupting enough association fibers to check the normal spread of nerve impulses and cause them to take a shorter, abnormal route, leading to explosive discharge. The essential difference is that the release theory deals in physiological levels as units, whereas the short-circuit conception may be used to explain an epileptic discharge from any anatomical lesion, whether large or small. The two, however, may well be combined. (4) The "Explosive" theory negates those enumerated above by holding that a seizure arises as a general wide-



spread change in brain tissue, not dependent upon spread of nerve impulses, but upon some sudden metabolic change—such as anaphylaxis, anoxemia or alkalosis.

None of these theories is alone satisfactory; probably all seizures are combinations of two or more of the four mechanisms. The first three have received the most attention, but modern research points to the last as perhaps the most fruitful field for future investigation. At the present writing it is the author's belief that epileptic seizures are neurological phenomena, usually motor, caused by some sudden change in the nerve cells. The etiological factors which might spring the trigger of this mechanism may be numerous and varied. These are discussed hereinafter. Nevertheless it aids in the comprehension of the problem if general etiology, precipitating factor, and neural mechanism of discharge are considered as mutually important, but different, phases of the total phenomenon.

### FACTORS INVOLVED IN CONVULSIONS

There are at least three factors which must be considered as of etiological importance in the production of seizures. They are (a) organic abnormalities in the structure of the brain or its coverings, (b) functional abnormalities in the cells of the brain that increase their "convulsive reactivity," and (c) abnormalities in the body outside the brain tissue. That functional instability of the brain must play an important part in persons with convulsions is clear when we remember that of persons having either organic brain lesions or marked disturbance in their body physiology, but a small proportion react to their abnormality by having epileptic seizures. Our conception of the situation is presented graphically by means of figure 4. In this schematic representation, all three factors are represented as sharing in each seizure. In the central figure there is no attempt to indicate the relative importance of each factor. This must vary enormously in different patients (as represented in the small figures at the side), and in the same patient from time to time. Thus, in any patient after the lapse of years, one would expect the intracranial factors to become more important and the extracranial factors less important. These three factors, of course, are intimately interrelated. In the

following pages taking figure 4 as a map (like the flat circular map of the ancient world) we shall explore the regions, known and unknown, which are indicated in it

#### PATHOLOGY OF THE NERVOUS TISSUE

The importance of any lesions of the brain or its coverings in the causation of fits is evident Foerster (1926) has listed the lesions of

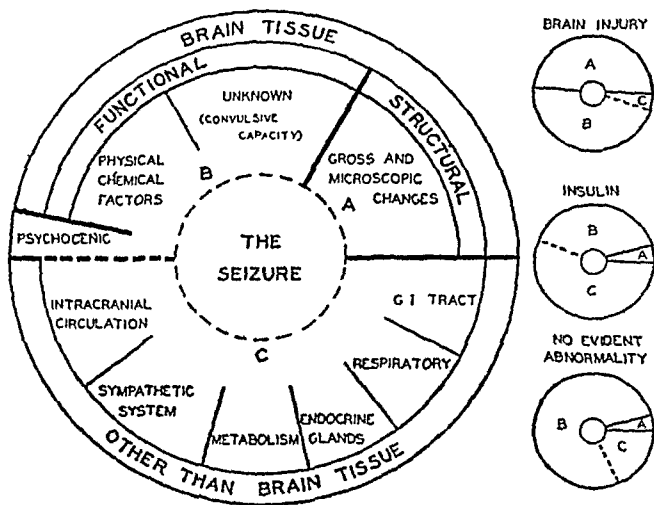


FIG 4 SCHEMATIC REPRESENTATION OF POSSIBLE FACTORS INVOLVED IN A SEIZURE

In the large circle there is no attempt to assign values to the various segments of the circle. The three small circles on the right represent three conditions associated with seizure. First, conditions of definite brain injury. Second, conditions in which body metabolism may be assumed to play an important part such as in the convulsions following over dose of insulin. Third, the hypothetical condition in which neither ante nor post mortem examination reveals abnormality in the body either within or without brain tissue, i.e., so-called essential epilepsy. In each of these three, segment B, representing functional instability, is assigned a large segment, for reasons given in the text.

the central nervous system which may be accompanied by convulsions as follows. Congenital brain disease, heredo-degenerative processes, traumatic lesions, tumor, parasites, syphilis, tuberculosis, cerebral

abscess, brain swelling, meningitis, leptomeningitis, chronic arachnoiditis, juvenile encephalitis, epidemic encephalitis, multiple sclerosis, presenile gliosis, senile cortical degeneration, toxins, and disturbances of circulation. As indicated above, such pathology alone does not cause epilepsy and hence cannot be the only factor involved. For example, convulsions occurred in only 4.5 per cent of 25,000 soldiers with wounds of the skull and in 30 per cent of 270 patients with tumor involving the brain,—Sargeant (1921). In 100 cases of brain tumor reported by Dowman and Smith (1928) convulsions occurred in 37. Less than one-half of infants who have cerebral birth palsies develop epilepsy,—Ford (1926). Again Thom and Southard (1915) found that patients with the more marked gross pathology were not the ones having the more frequent seizures. These statistical data are of value in showing that abnormalities present at birth or those associated with increased intracranial pressure are especially liable to be followed by convulsions.

#### *Evidence from post-mortem examinations*

*Macroscopic.* Concerning the size of the brains of patients with seizures, Munson (1918) compared the weights of 245 brains of epileptics that showed no organic lesions with the weights of normal brains. Up to the age of 25 the brains of epileptics were much lighter, after that age the weights were approximately the same as the normal group. Munson takes this to mean that the epileptic patients with light weight brains died early. Ganter (1922) found that in 161 epileptics the volume of the skull and weight of the brain were greater, on the average, than in 101 feeble-minded. The brains of epileptics dying in status were relatively heavier. Lind (1926) in 178 congenital epileptics found that the average brain weight of the idiots was less than the average weight of those not congenitally insane.

The gross lesions found in persons with epilepsy depend very largely on the class of patients examined. Autopsy reports in large groups of patients with epilepsy have come only from institutions which care for mentally deteriorated, chronic patients. Gross lesions in such groups are frequent, e.g., 63 per cent of 205 brains, Thom and Southard (1915), 34 per cent of 715 brains, Munson (1918), 89 per cent of 103 brains, Gregory (1919).

There is not a predominance of any type of lesion found in these brains. The data presented in table 1 are abstracted from the last eight annual reports from the Craig Colony for Epileptics of Sonyea, New York, and from observations by Lind (1926) in Australia. Because of different methods of classifications used in these reports and because of possible duplications in the listing of lesions, the percentage of abnormalities are only approximate.

TABLE 1  
*Gross pathology found in the brains of institutional epileptics*  
(718 at Craig Colony and 259 in Australia)

CONDITION	PERCENTAGE	
	Craig Colony	Australia
Dura—evidence of inflammation	12	38
Arachnoid—evidence of inflammation	10	45
Subarachnoid hydrops	13	
Brain—cerebral sclerosis	14	24
Hemiatrophy	10	6
Softening	13	6 5
Tumors	2	3 5
Porencephaly	2	6
Arteriosclerosis	6	9
Hemorrhage	8	
Edema	27	
Gumma	0 3	
Ventricles—assymetry	3	
Dilatation	12	52
Choroid plexus—cystic	3	2 7
Sella turcica—abnormality	9	

Lind apparently does not list certain abnormalities. The ones which he does mention occur more frequently than in the Craig Colony series. Presumably this is due to the use of different standards for normal. For example, before exclaiming over the fact that dilated ventricles are four times more common in Australia than in New York, one needs to know what, in the minds of the different pathologists, constitutes a dilated ventricle. That only 2 and 3 5 per cent of the patients were found to have tumor of the brain is of interest. These

figures closely correspond to those of Volland (1910) who in 150 cases found previously undiagnosed tumor in 3 per cent

It is to be regretted that the authors do not give figures showing what proportion of the brains were normal in appearance, and whether microscopical examinations were carried out

Although quite different in interpretation, Dandy's (1923 and 1927a) observations on the pathology of epilepsy at operation are corroborative of Lind's at necropsy. Dandy is able to demonstrate in the acquired cases (i.e., those cases which do not come under the heading of congenital malformation of the brain) a very striking gross pathology, consisting of dilated subarachnoid spaces forming pools of fluid and overlying small convolutions which are soft on palpation. On deeper exploration or by ventriculography, dilatation of the ventricles could be demonstrated. "At operation these changes in the subarachnoid spaces are strikingly evident to the naked eye. At autopsy they are very poorly or not at all evident. The reason is that when the fluid is lost, as at autopsy, the arachnoid membrane collapses on the brain and very little is to be seen." The loss of brain tissue is mostly in the white matter of the brain which is softer, less resistant to trauma and much easier of absorption than the gray matter. The changes in the subarachnoid space are an effect and not a cause. The cause of this type of epilepsy is the primary cerebral lesion. Tilmann (1926) states that he found pathologic changes on the surface of the brain in all his operated cases. He does not particularize.

These observations at autopsy and at biopsy are certainly important, and have an added interest when correlated with the experimental work of Dandy and Elman (1925) who showed that cortical injury lowered an animal's threshold for absinthe convulsions, and with the work of Speransky (1926) who by freezing areas in dogs' brains caused areas of sterile "encephalitis" which degenerated and gave rise to epileptiform seizures.

The important question arises as to whether the observed pathology is the cause of the epilepsy or only a result of repeated seizures, perhaps it even bears no relation to them. It would seem probable that some of the abnormalities observed, particularly dilated ventricles, marked sclerosis of the cornu ammonis or areas of softening from hem-

orrhages, might well be a result of repeated severe convulsions. We are endeavoring to collect autopsy reports from a large group of non-institutional patients, tabulating the data with respect to duration and severity of symptoms, the patient's mental condition and neurological signs before death, etc. On neurological examination the majority of institutional patients present clinical evidence of cerebral lesions. In contrast, only a comparatively small proportion of patients seen in private or dispensary practice show such evidence. This leads one to believe that only a minority of this latter group of patients would show structural abnormalities of the brain at autopsy.

Bagley's (1925) work is perhaps even more suggestive, for he found that puppies, to which he gave subarachnoidal injections of their own blood, weeks later might have chronic fits and develop internal hydrocephalus. Much more research is needed along all these lines before conclusions as to pathogenesis may be drawn, but the investigators must pause and realize that the riddle is not solved until those cases with chronic fits and no gross cerebral lesions are explained. Moreover, only a few of the patients with severe brain injury eventually become epileptic. The extensive cerebral wounds inflicted in the war must have undergone organization and gliosis with the formation of arachnoid cysts, yet Collier (1924) states that only between 5 and 8 per cent of these patients became epileptic. Stenthal and Nagel (1926) in 639 cases with gunshot wounds of the brain found that epilepsy resulted in 29 per cent. Of 500 soldiers with skull injuries followed by Villaret and Bailby (1927) 7 per cent developed convulsions. Reichmann (1927) in 603 cases with fractures of the skull and resulting lesions of the brain found that convulsions had occurred in 3.8 per cent. In these traumatic cases it is of interest to know that convulsions may not begin until years after the injury.

*Microscopic* Because gross inspection of the brains of persons subject to seizures has shown no constant abnormality, there has been a persistent search for lesions which might be revealed by the microscope. The older work is well summarized and discussed by Jakob (1914).

More recent observations are as follows. Bratz (1920) states that in 50 per cent of patients with epilepsy and in 25 per cent with general

paresis there was sclerosis of Ammon's horn. Apparently this was not a result of seizures for in cases of short duration and those having only petit mal, similar changes were found. No sclerosis was found in 16 children dying in convulsions. Kogerer (1923) in 2 cases found widespread fatty degeneration of the pyramidal cells of Ammon's horn. Weimann (1924) considered lesions of Ammon's horn neither typical nor pathognomonic. Westphal and Sioli (1921) described ganglion cells in the brain which contained corpora amylacea. These inclusion bodies were most numerous in the thalamus, nucleus ruber and nucleus dentatus. Takeuchi (1922) described the occurrence of small pale staining bodies in brains of children dying of convulsions. He states that similar changes were found in poisoning with ammonium chloride. Geitlin (1923) considers an incomplete form of cortical tuberous sclerosis of embryonal origin as the lesion responsible for epilepsy.

Spielmeyer (1924-1926) writes on the histopathology of epilepsy saying that the different brain changes found after a fit have no especial interest for they are also seen in other conditions, for example in acute brain swelling. The focal lesions, on the other hand, have a pathogenetic significance for they are characteristic in form and position and have been found in 80 per cent of 126 epileptics. They are small circumscribed areas of destruction occurring usually in the Ammon's horn and cerebellum. In recent lesions there is merely a focus of tissue destruction like a small softening, later there is a gliosis leaving punctate sclerotic areas. In the cerebellum there is a dropping out of Purkinje cells and in long standing cases with summation of lesions distinct atrophy may be discovered. Such lesions are frequently overlooked. The changes in Ammon's horn are similar. Out of 36 cases of status epilepticus he found 6 with especially acute lesions, which were evidently the precursors of the Ammon's horn sclerosis. The lesions were in the same location where gliosis appeared later. He could follow the fading and shrinking of the nerve cells, and the glia reaction around them as they went to pieces. The picture is that of an ischemic destruction, cell degeneration, lipid products of degeneration and gliosis. It is also important that the lesions are similar in distribution to those of arteriosclerosis and

endarteritis, there seems to be a local circulatory factor both in the cornu ammonis and cerebellum. The specimens, however, give no clue as to the cause of the ischemia, so Spielmeyer thinks it must be a functional circulation change—a vasoconstriction—for the changes coincide with those caused by angiospasm and there is nothing to indicate vasodilatation or stasis. He believes that the local lesions in Ammon's horn and the cerebellum are therefore the morphological results of angiospasm.

These changes are not expressed in the clinical symptomatology. They give us no etiological point of departure. They are to a certain extent only incidental findings which give us insight into the sequence of events of the encephalic pathological process.

#### *Evidence from clinical examination*

Observations concerning the pathology of the brain during life are limited to neurological examination, to study of the pressure, volume and contents of the spinal fluid, to ventriculography, and to direct observations made at the time of operation. We shall speak elsewhere concerning observations on the spinal fluid.

*Neurological examinations* Although a careful neurological examination often gives valuable information concerning lesions of the central nervous system, apparently a survey of the neurological findings in a large mixed group of patients having convulsions is lacking. Hodskins and Yakovlev (1927) in a detailed examination of 300 institutional patients found a positive Babinski sign constantly present in 29 per cent (bilateral in 11 per cent—unilateral in 19 per cent). There was evidence of injury of the pyramidal tract in 55 per cent, of extra pyramidal lesion in 28 per cent, and in only 17 per cent was the neurological examination negative. A survey of a non-institutional group undoubtedly would give very different results. Osnato (1923) for example, in 57 private patients found abnormal neurological signs in only three.

Recent reports concerning certain phases of a neurological examination are as follows. Aguglia (1922) in 19 patients did not find a reaction to the Barany test between seizures, whereas just before a seizure



nystagmus could be produced with the use of 15 to 45 cc of water. Focher (1925) found asymmetry to Weber's test of tactile sensibility in 30 per cent of the patients examined, and in 66 per cent of those who had had convulsions for more than five years. He thinks that this may be a manifestation of an asymmetrical development of the cerebrum or of secondary organic changes in the cortex. Apparently his observations were not controlled. Lillie (1925) in 60 patients with proved temporal lobe tumor found convulsions were the most frequent symptom. He localized the tumor by means of perimetric examination of the visual fields in 43 or 70 per cent of the patients.

*Ventriculography.* The field of ventriculography has been opened but recently. Foerster (1925) made observations of 11 patients with epilepsy, in whom because of the focal nature of the seizures, organic lesions might be expected. All of the films showed abnormality of the brain. Most commonly there was dilatation of the ventricles with asymmetry in size and position or loss of cortical substance, as shown by an accumulation of air over the surface of the brain. This evidence often furnished a clue to the area to be explored. In several instances excision of the cortical area involved resulted in suppression of the seizures. Wartenberg (1925) described the technique in detail and the observations on one patient with epilepsy. Tyczka (1925) in 18 examinations obtained abnormal pictures in all but two. Schuster (1926) used the method in 7 patients, Fischer (1926) in 6, and Carpenter (1927) in 24. Dandy (1927), the originator of the procedure, has found the method of considerable use in studying the brains of epileptics. We have spoken of the observations of Dandy and others at the time of operation.

### *Summary*

Though gross lesions of the brain occur in most institutional cases, the lesions found are not constant and may be the result rather than the cause of seizures. On microscopic examination, areas of degeneration in Ammon's horn are often present. In life, careful neurological examination supplemented by ventriculography may indicate organic lesions in the majority of institutional patients. No specific lesion of the nervous system in epilepsy has been demonstrated. Con-

vulsions occur in only a small proportion of persons with gross lesions of the brain. Almost any lesion plus the unknown  $X$ , which we call functional instability, may result in epilepsy. Reports concerning the brains of the non-institutional type of patient are needed

#### FUNCTIONAL ABNORMALITIES OF THE NERVOUS TISSUE

This is the terra incognita of all who have attempted to chart the problem of epilepsy. As we have pointed out in previous sections, even in the presence of brain lesions or of physiological abnormalities elsewhere in the body, an additional factor, such as undue tendency toward a convulsive reaction, is needed to explain the fact that seizures come only to certain individuals. In patients who present no abnormalities on careful antemortem and postmortem examination, the importance of this factor is yet more evident. In the words of Kussmaul and Tenner (1859) "Every physician of the present day who is at all judicious will relinquish the hope cherished with childlike confidence by certain schools and times, that pathological anatomy is destined to give an explanation of the nature and seat of epilepsy, and he will only expect that result from the progress of the experimental physiology of nerves." The problem is not unique for convulsions. Individual variation in the manner of reacting to environment is a characteristic of living matter. In the presence of a given stimulus, only certain individuals will react with a convulsion. This is no more mysterious than the fact that only certain individuals are "susceptible" to a given infection, or to cancer. Convulsions, though more dramatic and attention compelling, are no harder to explain than certain other more common neurological symptoms, such as sleep and headache.

The tendency to convulsive reaction on the part of nerve cells may be an inherent property of the cell that is beyond present analysis. At this point, a clearer knowledge of the place of inheritance in epilepsy would be of value. We point out later that the evidence for inheritance is far from conclusive. On the other hand, evidence recently gained shows that a portion of this "reactibility" can be analyzed. The proof of an intimate relationship between seizures and physico-chemical alterations in the body points to the importance of measurable

physical factors in the reactive capacity of nerve cells In figure 4 we have divided the factor of functional abnormality of nervous tissue into these three parts, viz, 1. An unknown, inherent (possibly inherited) reactive capacity. 2. A reactivity which is related to physico-chemical changes, and 3, to the emotional life Concerning the first, we have no information Observations relating to the second and third follow

### *Effect of physico-chemical changes in nerve cells*

The various factors that follow are but a few of the numerous interlocking parts of a whole What effects one, effects all, so that it is difficult or impossible to say that any one factor is of fundamental importance. The following observations deal mainly with experiments on animals. Indirect evidence gained from clinical studies will be presented in later sections, and the whole matter will be summarized in the conclusion.

*Oxygen consumption.* Like all tissues, the central nervous system is dependent for its proper activity on a continued and adequate supply of oxygen. Indeed Loebel (1926) has shown that the oxygen consumption of brain tissue, when compared with other tissues, is high Anoxemia of the brain, if severe enough, is regularly followed by convulsions Although we lack any extensive evidence, it is possible that oxygen lack is the common denominator of many diverse conditions which result in seizures, such, for example, as polycythemia and sudden anemia, or alkalosis and hypoglycemia Seizures which occur during sleep, when all the body functions are presumably running smoothly, are difficult to understand A possible explanation is the lowered oxygen consumption which occurs in sleep, especially if one may make the not improbable assumption that in sleep oxidative processes in the brain are disproportionately reduced Clinical demonstration of the importance of this factor is shown in observations detailed under oxygen consumption (see figs 5 and 7) In several of our patients seizures could be regularly induced by breathing oxygen poor air. Over-ventilation which also regularly produced seizures, would have no effect if the patient breathed an oxygen rich atmosphere (see fig 8). This is in line with the observation that in guinea pigs

strychnine convulsions are prevented if the animals are placed in an atmosphere of oxygen. Syz (1926) has found that if frogs are placed in an oxygen free medium (boiled water, oil or nitrogen) the convulsant reaction to injection of acid fuchsin is greatly increased. Campbell (1925) injected air under the skin and in the peritoneal cavity of rabbits and measured the  $O_2$  and  $CO_2$  tension of the gas after experimental procedures. He found that the  $O_2$  tension of the gas was increased after seizures induced by tetany and convulsant drugs, and argues that a decreased  $O_2$  tension in the cells of the brain was the immediate cause of such seizures. With the further use of the Warburg method for measuring the metabolism of excised tissue, we may gain new information concerning the intensity of the oxidative processes in the brain in various conditions. Myerson (1927) draws blood from patients from the carotid artery and the internal jugular and the arm veins. Comparison of blood from these loci may yield new evidence concerning relative metabolic processes in brain and muscle.

*Ionic equilibrium.* As we show elsewhere, the equilibrium of electrolytes is of undoubted importance in seizures. Interesting clinical evidence is presented under acid-base relationships. Although this subject offers opportunity for speculation, we must await more complete knowledge of the action of the various ions on protoplasmic activity. We may hope for information on this point from fundamental investigations being made by Reznikoff and Chambers (1927) on the reaction of amoebae to the intracellular injection of various salts, and by Millard Smith (1927) on the effect of various ions on the solubility of gelatine. Haldi, Routh, Larkin and Wright (1927) observed the effect of various anions and cations on the absorption of water by brain tissue. They found little absorption with calcium and much swelling with chloride. Different parts of the brain were affected differently. Unfortunately, they did not control the pH of the solutions with which they worked. Flesch (1917) has speculated concerning the mechanism of convulsions based on the conception of the brain cells as storage batteries containing the various electrolytes, of which NaCl is the most important. The discharge of the nerve cells depends on the concentration of electrolytes and on the resistance of tissues, which in turn depends on the temperature, the pH of tissues, the permeability of cell membranes, etc. He suggests that such a con-

and convulsions. This interesting observation deserves further study.

*Chemical constituents.* Recent investigations of the chemistry of the brain substance in patients with epilepsy are almost entirely lacking. Trétiakoff and Caesar (1926) reported an intense reaction for iron in the cortex of patients with general paralysis and a faint reaction in those with epilepsy. Observations concerning the glycogen content of the brain will be taken up below.

### *Evidence from effect of drugs*

It is obvious that our knowledge would be advanced if we knew the mechanism by which certain drugs cause and other drugs prevent convulsions.

*Convulsants.* Apparently little is known of the mechanism by which such convulsant drugs as cocaine and camphor act. Because the convulsant effect of insulin has greater clinical interest, it has received recent attention.

Cori and Cori (1925) and Holmes and Holmes (1925) found no decrease in free glucose of the brain in animals with insulin hypoglycemia but without convulsions. Asher and Takahashi (1924-1925) found that the glycogen content of the brain and the heart was much more stable than that of other tissues. The injection of insulin in rabbits if not followed by convulsions resulted in a slight increase of carbohydrates in the brain, whereas if convulsions ensued the brain glycogen was reduced by 80 per cent. Marked reduction also accompanied convulsions induced in other ways by picrotoxin and by tetanus. Their observations would seem to show quite clearly that the glycogen of the brain was drawn on only in conditions associated with marked excitation of the central nervous system. The exact relationship of such glycogen loss to the convulsions, whether cause or effect, is not as yet clear.

*Anti-convulsants.* Concerning luminal, Gruber and Roberts (1926) in perfusion experiments on the head of the dog found that the addition of 50 to 100 mgm. of sodium luminal to the perfusion liquid caused dilatation of cerebral vessels as measured by the rapidity with which the fluid flowed from the brain. If the beneficial effect of luminal is

due to increased circulation in the brain, one might expect good results from other drugs having the same action. This, in fact, is the explanation given by Karger (1924), Pethe (1925) and Peritz (1926) for the beneficial results which they obtained in certain patients whom they treated with caffien. The last named author used from 6 to 9 grams a day.

Gruber and Baskett (1925, a and b) found that phenobarbital had a depressing action on the heart. Its use in animals caused a fall of blood pressure and a slowed rate and increased depth of respiration. Bigwood (1924b) believed that the beneficial effect of luminal was due to acidosis. This opinion, however, would seem to be without sufficient experimental basis for the change in pH of the blood in the few cases who were given luminal was no greater than in other patients who received no luminal. Arnell (1926) states that phenobarbital sodium is without influence on the sympathetic and parasympathetic nerves. We review the evidence concerning the effect of the acid forming salts, ammonium and calcium chloride under acid-base relations.

Gartner (1926) observed that specially stained sections of brains of animals which had been poisoned with sodium bromide showed a localization of bromide in the protoplasm of the glial cells. Mott, Woodhouse and Pickworth (1926) administered barbitone to cats and monkeys by mouth. Masses of a peculiar mucinoid material, from 5 to 60 microns in diameter, were found distributed throughout the central nervous system. Chromatolysis, loss of Nissl substance, and signs of cell degeneration were present in the nerve cells after intensive treatment with any of the hypnotic drugs. The mucinoid material, as Wolff and Reed (1928) have demonstrated in morphine poisoning in dogs, represents a degeneration of the oligodendroglial cells.

It is possible that the effect of an anti-convulsant drug may be due in part to the action of the drug on the wall of the capillary, making it more permeable. This is suggested by the experiments of Krogh (1924) in which a solution of Veronal Sodium applied to the web of a frog permitted subsequent application of pituitrin extract to exert its characteristic constrictive effect.

More study of the mechanism through which anti-convulsant drugs

act is urgently needed. If sedative drugs cause microscopic changes in nervous tissues, this may explain certain microscopic changes that have been ascribed to epilepsy, and may be further evidence against the use of such drugs

### *Summary*

The hope for an understanding of convulsions lies in a knowledge of the factors which affect the reactive capacity of nerve cells. Additional information is needed concerning physico-chemical changes in nervous tissue. Fragmentary experimental evidence presented here in addition to clinical evidence in later sections, indicates that conditions involving changes in oxidation, in equilibrium of electrolytes and in acid-base elements, in permeability of cell membranes and in edema of tissues, may profoundly effect the liability to convulsions. In such changes the circulation plays an important rôle.

### *Psychogenic*

In all ages, a certain group of persons have believed that the origin of seizures lay outside the realm of the physical. Hippocrates argued that this "sacred disease" was not, as was commonly believed, an evidence of *divine possession* on the part of various members of the god family, but like other diseases, was due to physical causes. In later centuries this idea was apparently lost and seizures became a matter of *demoniacal possession*. The rise of medical science again put them on a physical basis. At the present time (both gods and demons being dead) many psychoanalysts consider seizures an evidence of *emotional possession*.

Clark (1926a) is the most prolific expounder of the psychogenic basis of seizures. He sees in convulsions a failure of adjustment to environment, an infantile unconscious striving after displeasure-pleasure pursuit ending in the final goal of a return to infancy, attended by the loss of consciousness and a convulsion. The essential epileptic, says Clark, is a pattern of the oral and anal erotic, he is ego-centric, emotionally inexpressive and excessively narcissistic. This produces a rigidity and inelasticity of the personality incompatible with flexible living, hence the explosive fit. This epileptic charac-

ter may be recognized before the onset of seizures Kennedy (1923) has made a caustic retort to these views In a fairly large series of epileptics, we have seen many who show none of the characteristics of Clark's epileptic personality Many, as Kretschmer (1924) points out, do show egocentricity and emotional poverty, but we look on these characteristics as a common result of chronic invalidism, or as accompanying symptoms, such as constipation or eyestrain, which may be minor contributing factors to the disease The concepts of "anal erotic" and "oral erotic" are so general and so applicable to a large part of the human race that it seems unlikely that they play any important etiologic rôle in seizures

Psychological factors in epilepsy are important, deserving a volume rather than a paragraph Many authors have given us interesting case reports of epileptics who in the aura preceding a spell live through an old emotional experience and who have been relieved by psychotherapy Rows and Bond (1926) have recently published some interesting case reports that compel attention and show that the psychological side must never be overlooked, especially in cases, such as those among soldiers, that come on after stressful periods in the lives of young adults Granted the importance of emotions in such individuals, we must yet remember that such stimuli in order to produce a convulsion must act through physiological processes—such as changes in blood flow through the brain or in the physico-chemical processes in nervous tissue Neither pin-worms embedded in the anal mucosa nor complexes buried in the personality are in themselves sufficient to produce a convulsion, though it is self evident that such inciting causes when present should be removed

The mental status of epileptics and the relation of their mental health to seizures is likewise an important subject which cannot receive adequate discussion here Ninde (1924) has applied the auditory memory span test to 2,000 epileptics in state institutions These patients as a group, had only one-half the memory span of normal persons The adults rated much higher than the children Ninde believes that mental impairment of these patients may not be due to the seizures, but to extraneous factors such as heredity, environment, or intellectual desuetude He points out that only  $3\frac{1}{2}$  per cent of the



epileptics in the United States are in institutions and that a survey is needed of the much larger and more representative group of patients who are scattered throughout the community. It is unfortunate that to the average person "epileptic" mean the helpless, deteriorated individual, commonly seen in institutions, rather than the person who, in spite of occasional attacks which are perhaps unknown to others, is carrying on his or her work in the world.

#### ABNORMALITIES OUTSIDE THE CENTRAL NERVOUS SYSTEM

##### *Consideration of sources of evidence*

*Clinical* The information thus far presented makes it clear that either lesion or functional instability of the central nervous system is present in most, if not all, of the persons presenting the syndrome called epilepsy. In spite of this consideration, it is important that we should know as clearly as possible what abnormalities exist in the body outside the central nervous system. It is evident that such abnormalities, if present, may be the inciting cause of seizures. Furthermore, a most important consideration, correction of such abnormalities may be the only available means of therapy.

Even superficial examination of the literature that deals with the metabolism or physiology of persons subject to recurring seizures, makes it evident that we are in need not of more theories but of more facts. A critical analysis of the facts that have been presented is important for several reasons. First, because epilepsy is classed as a neurological disease most of the investigators have been neurologists trained in pathological anatomy rather than in physiology and biochemistry. Second, modern laboratory methods have been developed only in the last few years and have been changing constantly. Many data that are still being quoted were obtained by methods now considered obsolete. Third, many of the investigations which have been reported were made on subjects confined to institutions. The abnormalities observed may not be the cause of convulsions, but the result either of the long standing convulsions or of the mental or physical deterioration present in many of these patients. Again in such patients who have had seizures for many years, the attacks may have become a habit, more or less independent of the original stimulus

Having demonstrated certain facts with regard to abnormalities in epileptic patients, one is confronted with the question of their significance, whether the relationship between seizures and observed abnormalities are causal or only casual. Many of the observations in the literature apparently belong to the latter group, for example, the statement that incidence of seizures varies with the tides (Brunner, 1916). Again, too often circumstantial evidence is given equal weight with direct evidence or sweeping generalizations are made from a few observations. It is our difficult task to separate foundation stones of fact from superstructure of theory. So many theories have been built based on insufficient and inconclusive evidence, and so many generalizations have been made from a few observations, that there is need for adherence to certain postulates, such as Koch set up in bacteriology. Thus we might question of any patient: Does he show variation which is clearly abnormal? Is this the only abnormality present? Did this abnormality precede the beginning of seizures? Is its correction accompanied by cessation of symptoms?

In the following review we shall endeavor to examine the evidence critically, presenting, when possible, data rather than conclusions. Because present laboratory methods have been developed only within the last ten or fifteen years, we shall confine ourselves largely to evidence presented within that period. In order that work already done should not be repeated, it is important to mention negative as well as positive findings. Remembering how often medical opinion has reversed itself in the past, we should maintain an open mind concerning facts which do not fit into our present conception concerning the causes of seizures.

It is plain that factors outside the central nervous system are only contributory to those within, and because a seizure is only a symptom, we must not expect to find any one abnormality which is common to all patients with seizures. In order to meet this confusing and difficult situation, any investigation which is undertaken should include a large group of patients of various types. The fact that some searchers have been careful to confine their observations to patients with "genuine epilepsy" has prevented them from seeing that the same abnormalities discovered in these, existed also in patients with focal epilepsy. It is also evident that any abnormality dis-

covered in only a small proportion of the patients examined may be of etiological significance in this small group

*Autopsy material* In view of the fact that hundreds of patients with epilepsy die each year in tax-supported institutions, it is strange that there are not large series of observations concerning the pathology to be found outside the central nervous system We have tabulated certain statistics from reports of the Craig Colony which will be presented later. Such data are incomplete because weights and microscopic examinations of organs are lacking.

### *The circulatory system*

*Heart* Patients with epilepsy do not have disease of the heart or arteries more frequently than other ambulatory patients In 423 autopsies at the Craig Colony, hypertrophy of the heart was found in 9 per cent.

Lewis (1923) found that 30 per cent of the cases with epilepsy had hearts weighing less than the average. As to the clinical association of heart failure and seizures, Oddo and Mattei (1919) in a review of the literature from the year 1743 onward, report 13 case histories in which incompetence of the heart was accompanied by seizures. In their own patients, seizures would seem to be more nearly related to cerebral arteriosclerosis than to heart disease Gruber and Lanz (1919) also present cases in which heart lesions were discovered in patients having convulsions Peritz (1926) noted "heart spasm" apparently the result of spasm of coronary arteries, as a precursor of seizures in some patients He assumes that there was an accompanying spasm of cerebral vessels

The association of loss of consciousness with heart block is well known The occurrence of convulsions is more rare. Kouwenaar (1917) has described a case in which the heart did not beat for a period of  $1\frac{3}{4}$  minutes and convulsions typical of epilepsy occurred Convulsions may be associated with paroxysmal tachycardia, as noted by Smith (1902), Perrero (1923) (a single case with gas poisoning), Sutherland (1927) two cases and Barnes (1926) The last named author has a series of 15 cases from the Mayo Clinic in which epilepti-

form seizures occurred with relation to paroxymal tachycardia. In several of these a diagnosis of epilepsy had been made. He looks on the symptoms as evidence of cerebral anemia.

With reference to the heart beat in patients without serious irregularities of rhythm, Russell (1906) describes a number of incidents in which there was a cessation of the pulse beat at the onset of seizures. Using graphic methods, Munson (1908) in 10 patients and Gibson, Good and Penny (1910) in two, found no such irregularity. Certainly in almost all patients changes in rhythm and rate which may occur with relation to seizures are effects rather than cause. We have obtained electrocardiograph records of patients during petit mal and myoclonic seizures. In these instances neither the rhythm nor amplitude of waves was appreciably affected

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*Capillaries* The newer work on the circulation demonstrates that the capillary bed opens and closes to meet the functional needs of the tissues. This throws the question of capillary circulation into new prominence. Apparently only two observations have been made in epileptics. Hirsch (1925) states that the capillaries in the nail bed of one hand of his patient showed marked variation in shape and increase in sizes. Eighteen months later, when seizures were greatly diminished, the capillaries in the two hands were equal. Olkon (1927) describes a patient having visible spasm of capillaries, both spasm and seizures being relieved by atropin. Hinselmann (1923) in 19 patients with eclampsia found capillary spasm and stasis in 90 per cent. After recovery the capillary circulation of these patients was normal.

*Blood pressure* Blood pressure in patients with epilepsy is dependent on their physical condition. Hartenberg (1920) gives observations in 80 patients. Marchand and Adam (1923) measured the blood pressure of 43 patients, three of whom had daily readings for periods of from 60 to 96 days. Reed's (1916a) ptotic patients had hypotension. During seizure blood pressure is greatly elevated and after seizure it is lower than before, probably due to exhaustion. Trentzsch (1924), using Schneider's method of neurocirculatory rating, examined 8 epileptics. They rated from one to ten, a poor showing.

It is possible that arterial hypertension, when it exists, as in patients with arteriosclerosis, may contribute to the production of seizures Poppelreuter (1918) observed that of 40 soldiers with head injuries, only those with systolic blood pressure over 135 mm. had convulsions

*Intracranial circulation* In a preceding section we have mentioned several factors which may effect the blood supply of the brain. Investigators have had no satisfactory means of measuring either the volume or the speed of blood flow through the brain. It has been discovered only recently that the proportion of open capillaries is constantly varying. That this is true of the brain as well as of the other parts of the body is indicated by the experiments of Cobb and Talbot (1927). Spielmeyer (1926) has suggested that the angulation of small vessels found in certain cortical layers of Ammon's horn may bear relation to the lesions found there. The work on changes in brain bulk and in cerebro-spinal fluid formation and absorption is likewise new. Therefore, speculation concerning intracranial circulation with relation to seizures has been concerned chiefly with the theory that convulsions may be caused by constriction of the cerebral blood vessels.

*Vasomotor control.* The theory of "vascular spasm" was discussed by Hughlings Jackson (1863) and by Gowers (1881) but neither of these great teachers took much stock in the idea. Since then the clinical evidence, though often inconclusive, has gradually accumulated until at present "vascular spasm" is a mechanism accepted by most clinicians as explaining transitory hemiplegias, aphasias and hemianopias. Such attacks, however, usually occur in arteriosclerotic patients, whose arteries may not be sufficiently elastic to permit much contraction. Another explanation is given by Fleming and Noffziger (1927) in an arteriosclerotic subject the blood supply through the narrowed vessels may be only just sufficient to support function. Under these conditions a temporary reduction in the systemic blood pressure may so decrease the blood supply to the brain that focal or general cerebral symptoms result.

In addition to the above mentioned conditions, migraine and epilepsy are often ascribed to spasm of the cerebral vessels. Richter (1925) discusses the subject in detail and argues that localized con-

traction of vessels in various parts of the brain may explain the various types of seizures observed. As corroborative evidence there are the direct ophthalmoscopic observations of changes in the retinal arteries. Hirschfelder (1914) has shown that the retinal and cerebral arteries constrict or dilate synchronously. Bramwell and McMullen (1926) and others have described alteration in the diameter of the retinal arteries during attacks of migraine. Jean (1926) told of a young man in whom he watched the repeated blanching of the retina, the cherry red spot in the macula appearing and disappearing during the ophthalmoscopic examination.

With regard to observations of the fundus oculi during a fit, Echiverria (1870) described the disc just before a convulsion as pale with indistinct arteries. Hughlings Jackson (1863) said the fundus was pale before a fit, but during the seizure the veins became large and dark. Many surgeons have seen the exposed cortex undergo vascular changes during epileptic attacks on the operating table. Kennedy (1923) described pallor of the brain before the convulsion, Horrax (personal communication) tells of pallor followed by congestion and bulging, while Foerster (1926) described a sequence of events repeatedly seen by him at the operating table: first, the brain becomes pale and sinks away from the skull, then it is suffused with blood and bulges greatly as the convulsion starts.

That the observed changes are due to vasomotor control of the cerebral vessels is by no means proven. Sudden variations in venous pressure due to changes in cardiac output and intrathoracic pressure could explain the observations as well or better. The experiments of MacDonald and Cobb (1923) illustrate this point. Properly to evaluate these observations one must realize that the skull is normally a closed box containing brain tissue, blood, cerebrospinal fluid, meninges and vessel walls. Pallor and falling intracranial pressure can be as well explained by a sudden drop in venous pressure as by active constriction of the arteries. Congestion and increased intracranial pressure can similarly arise from either active vasodilatation or increased venous pressure, as in jugular compression. Less acute changes may be explained on the basis of cerebral edema or increased amounts of cerebrospinal fluid.

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In addition to the above mentioned conditions, migraine and epilepsy are often ascribed to spasm of the cerebral vessels. Richter (1925) discusses the subject in detail and argues that localized con-

traction of vessels in various parts of the brain may explain the various types of seizures observed. As corroborative evidence there are the direct ophthalmoscopic observations of changes in the retinal arteries. Hirschfelder (1914) has shown that the retinal and cerebral arteries constrict or dilate synchronously. Bramwell and McMullen (1926) and others have described alteration in the diameter of the retinal arteries during attacks of migraine. Jean (1926) told of a young man in whom he watched the repeated blanching of the retina, the cherry red spot in the macula appearing and disappearing during the ophthalmoscopic examination.

With regard to observations of the fundus oculi during a fit, Echiverna (1870) described the disc just before a convulsion as pale with indistinct arteries. Hughlings Jackson (1863) said the fundus was pale before a fit, but during the seizure the veins became large and dark. Many surgeons have seen the exposed cortex undergo vascular changes during epileptic attacks on the operating table. Kennedy (1923) described pallor of the brain before the convulsion, Horrax (personal communication) tells of pallor followed by congestion and bulging, while Foerster (1926) described a sequence of events repeatedly seen by him at the operating table: first, the brain becomes pale and sinks away from the skull, then it is suffused with blood and bulges greatly as the convulsion starts.

That the observed changes are due to vasomotor control of the cerebral vessels is by no means proven. Sudden variations in venous pressure due to changes in cardiac output and intrathoracic pressure could explain the observations as well or better. The experiments of MacDonald and Cobb (1923) illustrate this point. Properly to evaluate these observations one must realize that the skull is normally a closed box containing brain tissue, blood, cerebrospinal fluid, meninges and vessel walls. Pallor and falling intracranial pressure can be as well explained by a sudden drop in venous pressure as by active constriction of the arteries. Congestion and increased intracranial pressure can similarly arise from either active vasodilatation or increased venous pressure, as in jugular compression. Less acute changes may be explained on the basis of cerebral edema or increased amounts of cerebrospinal fluid.



in the systemic arterial and venous pressure, they also add convincing data to the already considerable evidence of Weber, Hurthle and others. Thus it is shown that Hill's experiments failed to prove the absence of a cerebral vasomotor mechanism.

In addition to experiments on nerve stimulation, much work has been done on the effect of adrenalin on the vessels of the brain. This, as a method for determining the presence of vasomotor nerves, is not entirely satisfactory, although such an authority as Gaskell (1916) says that the action of adrenalin has proved the existence of vaso-constrictor nerves in the brain. Schilf (1926) is of the opinion that the action of adrenalin in itself cannot be used as a proof of the presence of vasoconstrictor nerves. Such interesting work as that of Wiggers (1905) who showed by perfusion of an excised brain that adrenalin decreased the outflow, should only be used as corroborative evidence of the existence of vasomotor nerves. The recent experiments of Gruber and Roberts (1926) explain the former conflicting evidence in this field, apparently the dilatation of cerebral vessels following application of adrenalin recorded by several observers was due to the use of acid solutions, or to chloretone. Pure adrenalin alkaloid causes vasoconstriction if the solution is not acid.

Summarizing the situation, Schilf (1926) says:

"The cerebral vessels contract after stimulation of the cervical sympathetic, equal effect occurring in the two hemispheres from unilateral stimulation. The peripheral nerve cell lies in the superior cervical sympathetic ganglion, so if one injects nicotine into it the vasoconstriction reaction to sympathetic stimulation is lost. There is no tonic activity, for cutting the cervical sympathetic does not affect the brain vessels. Moreover, stimulation of the nervous depressor vagi causes no reflex dilatation of brain vessels. This makes the vessels unique."

If we add to this the evidence brought forward by Forbes and Wolff that vagus stimulation causes dilatation of the cerebral vessels, and modify Schilf's statement that "there is no tonic activity," the evi-

dence being conflicting, we realize that blood vessels in the brain react to stimulation and to some chemical substances in the same way that vessels in other organs of the body react. It is probable, however, that they react less strongly.

The last statement quoted from Hill, to the effect that no nerve fibers have been found going to cerebral vessels, has been proved erroneous. In fact, Gulland who did the histological studies for Hill in 1895 and found no nerves, published a paper in 1897 retracting his statement and showing that nerves are present. In a letter to Dr J W Courtney in 1899, Gulland says "I am afraid there is no doubt about the nerves on the intracranial blood vessels. Their actual distribution and arrangement are very much the same as those on other vessels, except that they are, perhaps, a little more scanty. I'm rather sorry I've found them for the discovery rather takes the legs from Hill's and Bayliss' work, but you may take it from me that *they are there*." We must remember, however, that histological methods do not differentiate between motor and sensory nerve fibers. Other investigators have also demonstrated these nerves. The most convincing publication, which contains a good review of the literature, is that by Stohr (1922). He gives beautiful illustrations of nerves and nerve endings on the fine pial vessels.

Taking all this evidence into consideration, it would seem that vasomotor control of cerebral vessels is now established. One must be guarded, however, in drawing clinical conclusions. Physiologically it has been shown that cerebral vessels may constrict and dilate in response to appropriate stimulation, but in anesthetized animals the changes are not of a great magnitude, and may be overcome by large variations in systemic pressures. Hill's fourth statement, strictly speaking, still holds. "There is no evidence of a causation of cerebral anemia by spasm of the cerebral arteries." Real obliterating angiospasm has only been seen when vessels are strongly and locally stimulated under non-physiological conditions—Florey (1925), Wolff (personal communication). Recent investigations, however, certainly make vascular spasm a much more reasonable working hypothesis than it was 30 years ago.

*Effect of sympathectomy.* Kussmaul and Tenner (1859) caused

convulsions in a rabbit in which one carotid was tied, by faradization of the cervical sympathetic on the opposite side. Apparently no such observation has been made in the monkey or in man.

If seizures are indeed due to vasomotor constriction of arterial vessels, one would expect that removal of the cervical sympathetic chains might prevent them. Such an operation, performed on 24 patients by Alexander (1889), has been used at intervals since. The results have been generally disappointing. Of recent authors, Wagner (1925) cites two cases without distinct improvement. Tinel (1925) gives a single case with absence of seizures for 6 months following operation as against several grand mal daily for the previous 3 years. Bojovitch (1925) found improvement in 3 operative cases. Babitzky (1925) suggests a combination of sympathectomy and decompressive operation of the skull but does not give the results from such treatment. Hirsch, Weiss, Izgur and Lauerma (1927) obtained improvement in 4 of 9 patients in whom sympathectomy was performed. This operation performed in dogs did not show changes in the subsequently injected intracranial blood vessels.

As Foerster (1923) suggests, sympathectomy should be confined to patients who show evidence of abnormal function of the cervical sympathetic system. In one such patient of ours, who had a well marked Horner's syndrome, which was exaggerated at the time of seizures, unilateral cervical sympathectomy was performed. For many months before the operation the patient had several seizures daily. For a week after the operation seizures were absent, then reappeared, later to disappear entirely. Mental condition was improved.

*Effect of vasodilators* Popea and Eustatzion (1927) in 16 patients found that inhalation of amyl nitrite averted or suppressed convulsions.

*Effect of carotid compression* Clinical observations concerning the effect of suddenly shutting off the blood supply to the brain have been made by many authors. Kussmaul and Tenner (1859) in six non-epileptic subjects produced convulsions in two by compression of carotids. Flesch (1915) produced typical seizures in three patients, one with generalized convulsions, one with Jacksonian epilepsy, and

one with hysteria Tsiminakis (1915) made observations of 30 non-epileptic persons, in all of whom compression of the carotids for one minute or less produced loss of consciousness without muscular twitchings In 116 epileptic patients loss of consciousness occurred not later than 30 seconds after compression, and "in a majority" seizures occurred which were lighter than uninduced seizures Patients suffering from Jacksonian epilepsy had the induced convulsions on the usual side Nine patients whose seizures were at infrequent intervals had no seizure after compression He gives 14 case histories but no detailed tabulation of the results with the whole group of patients Compression was also practiced in 42 cases of hysteria These patients said the resulting seizures were similar to spontaneous spells Loewy (1916) on the other hand, failed to produce seizures

These observations, together with experimental work on animals by many authors, show that deficient blood supply to the brain may be associated with fits The rationale of decreasing blood supply as a therapeutic measure is not clear Nevertheless, various authors have reported improvement in patients following permanent compression or ligation of certain arteries to the brain Alexander (1889) ligated both vertebral arteries in 36 patients, of whom eight were "practically cured" One or both carotids have been ligated with benefit by the following authors Parker (1907), one case, Momburg (1914), two cases, and Eastman (1915), three of six cases

*Summary* With the demonstration that cerebral arteries are under vasomotor control, the old conception that fits are the result of vascular spasm stands in the foreground Final proof is lacking Study of this and other phases of the blood supply to nerve cells should be a rich field for further exploration

#### *Autonomic nervous system*

The chief interest in the autonomic nervous system lies in its relation to vasomotor control of cerebral arteries This has been discussed in a previous section If there is a disturbance of the cervical sympathetic system in epileptics, as some authors believe, we should expect evidence of disturbance in other portions of the system

Guillaume (1922) described dermographic reactions of the skin

which became pronounced following a seizure and which coincided with a fall of blood pressure Loewy (1922) considers that both migraine and epilepsy are expressions of disorder of the vegetative nervous system Bolten (1924) ranges yet farther afield He believes that the edema of urticaria, asthma, migraine, dysmenorrhea and epilepsy is due to vasomotor disturbances that are induced by circulating toxins Therapy by means of protein injections acts by paralyzing the sympathetic system Langeron (1925) describes the various symptoms in epileptics that result from a disturbance of the sympathetic system. Tracy (1926) in a collection of previous scattered publications reiterates his belief that essential epilepsy is a disturbance of the sympathetic nervous system As evidence for over-active vasoconstriction, he states that the white line which follows stroking of the skin occurs more quickly in epileptic persons than in others, and that epileptics show the presence of permanent small white spots on arms, hands or face These spots were present in 71 of 79 institutional patients examined and were "invariably" found in "hundreds of cases" examined since They may antedate the onset of convulsions He does not state in what proportion of patients the paralyser of the sympathetic system which he uses (*oenanthe crocata*) is effective in decreasing seizures

Clearly vasomotor over-activity, as evidenced by areas of cutaneous vasoconstriction, cannot be held exclusively responsible for seizures, because many healthy persons present white spots similar to those which Tracey describes Their number is too great to permit the assumption that they are in the preconvulsive stage of epilepsy.

*The vagus* Concerning the effect of paralysis of the vagus, Popea, Eustatziu and Holban (1925) in 45 patients applied tests with atropin combined with change of posture A seizure resulted within 10 minutes in 6 subjects, within 30 minutes in 1 and within 20 hours in 15 The degree of cardiac slowing which attends compression of the eyeballs has been used as one test of the degree to which the vagus may be stimulated Roubinovitch and Chavany (1921, 1923) applied the test in 80 patients, 25 of these showed a slowing of more than 25 beats Because the results were inconstant, they lay stress instead on the tachycardia which occurred after the release of compression in 50 of

the 80 patients Vergara (1922) found either increase or decrease in the oculo-cardiac reflex after seizures but not in the interval between Marchand and Adam (1923) examined 43 patients of whom 46 per cent showed a bradycardia during pressure and 48 per cent a residual tachycardia, results which did not differ greatly from the response of normal subjects. Abnormality was less frequent in patients taking luminal. Claude, Tinel and Santenaise (1923) made graphic records of results. The epileptic patients showed marked variation from time to time. In patients having frequent seizures, the reflex was most increased. It was increased before a seizure and normal or inverted after. Tinel and Santenaise (1924) report two patients who had an active oculo-cardiac reflex. Bolten (1924) considers the test important. Felsani (1924) considers the pure epileptic vagotonic while others consider him sympathetocotonic.

These various observations viewed separately do not appear important. Taken as a whole, however, they indicate that many patients with epilepsy present evidence of a lack of balance of the autonomic system. Such demonstration is important because of the possible causal relationship to seizures through alteration in the blood flow of the brain. This is a phase of the problem that is of major importance and that deserves thorough study. Because the autonomic system is so protean in its manifestations, observations should be comprehensive, dealing with such various factors as capillary permeability, intensity of vasomotor reactions, response to various drugs, and the presence of such symptoms of autonomic imbalance as cyanotic extremities, sweating, flushing, excessive lacrimation or salivation, frequent urination, constipation or diarrhea, sinus arrhythmia, unusual skin reactions, skin pallor as a precursor of seizures, etc. Such a survey must, of course, embrace healthy as well as epileptic subjects, and to carry conviction must record all the tests on all the subjects. At present the literature is encumbered and confused with reports of a few cases only, or with reports of one test, only, on a series of cases. The large number of patients who give evidence of instability of the sympathetic nervous system makes it desirable that measures or medicines should be found which would allow better control of the circulation in the small blood vessels of these patients.

*Respiration*

The cessation of respiratory movements during the tonic phase of a convulsion and the violent breathing which follows is, of course, familiar to all. Few attempts have been made, however, to make graphic record of the sequence of events, or to study the respiratory metabolism. Echeverria (1870) noted a decreased respiratory rate with reference to pulse rate in 40 patients. He believed that this denoted insufficient oxygenation of the blood. Knauer (1910) recorded respiratory movements by means of a belt about the chest during convulsions of a child. Scripture (1924) and others have emphasized the monotony and stiffness of speech of epileptics, an expression apparently of muscular rigidity. Bornstein (1911) conducted interesting experiments with 5 patients whom he caused to breathe abnormally high concentrations of  $\text{CO}_2$ . He used a Zuntz Geppert apparatus, and expressed results as liters of air respired for each per cent of  $\text{CO}_2$  in the expired air. He found considerable variation in the response but in general a decreased excitability of the respiratory apparatus to stimulation by means of increasing concentrations of  $\text{CO}_2$ . Hundreds of observations were made of these patients, but sufficient control evidence is not presented of the response of healthy persons to the same test. Arnoldi and Ferber (1923) observed a diminution in the minute volume of respiration in a patient before a seizure. Lennox (unpublished data) has made hundreds of graphic records of the pulmonary ventilation of epileptic patients. Many of these show marked irregularity in the rate and depth of breathing. The records have not yet been thoroughly checked against those obtained from a group of healthy subjects. During petit mal there was either no change or an increased depth of expiration. Records made during short myoclonic seizures are shown under oxygen consumption (see fig 5). Information gathered from a study of the respired gases will be discussed under oxygen consumption and metabolism of food material.

Pulmonary infection ranks high as a cause of death among institutional patients. Such infections are a complication rather than a cause of convulsions.

*Gastro-intestinal tract*

Abnormalities of the gastro-intestinal tract have been frequently accused of playing a prominent part in seizures. Clinical grounds for this are seen in the inordinate appetites and the constipation which many patients show, also in the improvement which often follows the regulation of the diet and the bowels. Although most clinicians agree to the therapeutic importance of a normal functioning of the gastro-intestinal tract, they differ widely in their statements concerning the incidence of intestinal abnormalities and the specific relation of such abnormalities to seizures. On the one hand many believe that the constipation is a result of the poor physical and mental condition of patients. Others, like Reed (1921) define epilepsy as "chronic convulsive toxemia" of intestinal origin.

*Pathology* Here, as elsewhere, our task is not that of weighing contrary opinions, but of presenting evidence. In what proportion of patients is there organic abnormality of the gastro-intestinal tract? The available autopsy reports show a surprisingly small proportion of abnormalities. Caro (1917, a and b) in 280 autopsies of institutional cases found intestinal adhesions and peritoneal bands in 18 per cent. This was the same percentage found in 775 non-epileptic patients autopsied at the Boston City Hospital. Caro, therefore, concludes that constipation in epilepsy is rarely due to congenital defects, but is from the same causes as in other patients. He believes that most of the adhesions found were the result, rather than the cause of stasis. We have tabulated data concerning certain abnormalities found in the last 423 autopsies performed at Craig Colony. The percentages of certain lesions were as follows: Dilated stomach, 5 per cent, inflammations of the small intestine, non-tuberculous, 9 per cent, tuberculous, 3 per cent, inflammation of the large intestine, non-tuberculous, 14 per cent, tuberculous, 1 per cent, enlarged mesenteric lymph-nodes, non-tuberculous, 9 per cent, tuberculous, 6 per cent. If one may accept these routine autopsy reports, epileptic patients show no greater degree of organic abnormality of the gastro intestinal tract than other types of institutional patients who have not been subject to convulsions.

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Reed (1916a) who states that 100 per cent of the operated cases presented dilatation of the duodenum and enlarged retroperitoneal glands. These patients were, of course, a selected group, referred to Reed for operation.

*Functional disorders* Observations made at autopsy give no information concerning the position of the gastro-intestinal tract during life or its function. Important information on these points may be gained by X-ray examination. Reed (1921) makes a blanket statement that all epileptics show splanchnoptosis as proved in his 810 consecutive examinations. The report of Harryman and Donaldson (1923) is very different. They examined 50 patients following ingestion of a barium meal. Twenty-five of these had hypermotility—usually of the colon, nineteen had a slight degree of stasis, and in none was there evidence of marked stasis. Two showed evidence of ulcer, one of ptosis, three of adhesions and thirteen of a chronic inflammation of the appendix. Bethea (1927) gives detailed observations in 400 institutional patients. Some of the abnormalities noted were, pyloric spasm 25 per cent, dilated stomach 28 per cent, spastic colon 16 per cent, colonic stasis 41 per cent, hypermotility of small intestine 40 per cent, spasticity 42 per cent. These results are indicative of autonomic imbalance but need comparison with similar data obtained from healthy persons.

Concerning gastric secretions in epilepsy, we have seen only the report of Felsen (1924). In 53 patients he measured the acidity of the gastric juice following the ingestion of water. In 15 per cent there was absence of free HCl. He was unfortunate in his selection of a control group, for the 19 per cent of non-epileptics who also showed absence of HCl were found later to be "quite likely" epileptic. One wonders whether these patients without free HCl had been on a meat free diet.

As previously stated, there is common agreement that patients with epilepsy are usually constipated. Yet even such a simple statement has not been verified by actual observation in a large series of cases. Nielson (1925) compared 200 epileptics with an equal number of non-epileptic patients. The percentage who were constipated was as follows. idiopathic epileptics, 87 per cent, symptomatic, 78 per cent, non-epileptics, 66 per cent. Unfortunately Nielson does not give his

criterion for constipation Vining (1922) stated that in 194 patients, one-third had a history of "bilious attacks" He had no control series

Although the direct evidence of organic or functional abnormality of the gastro-intestinal tract in epileptics is surprisingly meager, there are a number of clinical reports in which the matter has been put to therapeutic test Robertson (1924) states that in 500 patients with chronic intestinal stasis, 27 had convulsions Fifteen of these 27 received adequate treatment Five were made free of seizures and all but four were improved Single case reports are given by Barclay (1917) and Block (1923) Kopeloff, Lonergan and Beerman (1925) fed 12 patients with a liter of acidophilus milk daily, in four, seizures were reduced Kaolin was given to another group without benefit In three patients with poor posture and x-ray evidence of ptosis of the stomach and transverse colon, Lennox and Brown (unpublished data) have seen complete cessation of seizures following orthopedic treatment for correction of the posture One child in the eleven months before the beginning of treatment had had 175 major and thousands of minor seizures A few weeks after the beginning of treatment, seizures ceased and have not reappeared in the five years which have elapsed since In such cases it is not clear whether benefit is due to relief of constipation, to improvement of intra-abdominal circulation, to increased ventilation of the lungs, or to decrease of fatigue as a result of improved musculature Possibly all are concerned

Axtell (1916) found angulation and fecal impaction of the sigmoid in 45 patients, 8 of whom became free of seizures following medical treatment A more drastic therapeutic measure is the surgical removal of a portion of the intestinal tract Reed (1916a and 1920) has performed hundreds of such operations on patients who presented the picture of toxemia (low temperature and blood pressure) and in whom he demonstrated ptosis, stasis, ulcerations of the colon and enlarged mesenteric lymph-nodes He is able to recite a number of instances in which relief of symptoms followed removal of a portion of the cecum or colon His contentions do not carry conviction because he does not state the proportion of patients benefited nor the operative mortality Armstrong (1926) reported two patients in whom there was cessation of attacks following colectomy On the other hand, Brewster (1922) performed colectomy on 12 patients without relieving any

In patients who do have chronic intestinal stasis, the part played by this stasis in causing convulsions is not clear. The opinion of Purcell (1702) is essentially that held by many clinicians to-day "When the Aliments are not well digested, they turn into Crudities, these Crudities by little and little gather together in the Wrinkles and Folds of the Stomach and Guts, where they lie for some time . . . till at last they are so dissolved and liquefied as to enter by the Milky Veins into the Blood, where they produce all these Accidents . . ."

We do not know whether such "crudities" or "toxins" are normal food products prematurely absorbed, are abnormal "split products," or are the products of bacterial growth Geyelin (personal communication) has injected an extract of the fecal material of patients into dogs with resulting convulsive reactions which were more marked than those obtained from the control material

Because of the widespread clinical opinion that constipation plays a contributory part in the production of seizures, investigation of the gastro intestinal tract should be a fruitful field for research We need controlled quantitative observations of the extent of constipation in epileptics, with data as to the beginning of this symptom in relation to the onset of seizures, also bacteriological and chemical studies of the contents of the colon in these patients

*Liver.* Theories concerning the mechanism of seizures occasionally include the liver in the chain of reasoning This is because of the rôle played by the liver as a detoxifying organ, as illustrated by the fact that dogs in which the portal blood is shunted around the liver have convulsions when fed meat Normally the weight of the liver is greater than that of the brain In 42 cases of epilepsy studied post mortem, Thom (1916) found that contrary to the usual condition, the brain was heavier than the liver in 62 per cent Apparently microscopic examination of the livers was not made. Lalor and Haddon (1920) in 25 epileptic patients found the average weight of brain and liver was in the ratio of 35 to 33. They believe that the fibrosis which they found was the result of continued toxic action. In 423 autopsies performed at the Craig Colony the proportion of cases showing certain conditions of the liver was as follows: Atrophy 0.9 per cent, hypertrophy 2 per cent, fatty liver 17 per cent, adhesions about gall bladder

4 per cent, cholelithiasis 5 per cent. Lind (1926) reports fibrosis of the liver in 64 per cent of 259 cases, apparently microscopic examination was not made. Because the liver is such an important organ, and because the above mentioned reports are so divergent, this question is worthy of more complete study. In eclampsia there is often evidence of decrease of liver function, as shown by deficient elimination of injected dyes. Dysfunction has been reported in migraine by Diamond (1927). We have seen no reports of liver function tests in epilepsy. The fact that blood fibrinogen in epileptics is oftentimes high may indicate the presence in these patients of some mild irritative condition of the liver.

*Summary.* A widespread belief that the gastro-intestinal tract plays a prominent role in seizures is not supported by convincing data in the literature. Apparently organic or functional abnormalities are not more common in epileptic than in other nervous patients. We are without direct evidence of a toxic substance arising in the intestines that may contribute to seizures. Presumably distension of the colon may cause nerve fatigue by over-stimulation of sensory nerves or it may be that the effect is due simply to the general physical fatigue and lowered physical fitness which oftentimes accompanies constipation.

#### *Basal metabolism (oxygen consumption)*

Abnormality in the amount of oxygen which a person consumes (in the absence of such conditions as inanition, fever, anemia and leukaemia) is usually an indication of endocrine disturbance. There are comparatively few observations concerning the basal metabolic rate in epilepsy. Boothby and Sandiford (1922) in 32 epileptics found that the rate in 23 per cent was below minus 10 per cent. Talbot, Hendry and Moriarty (1924) in 11 epileptic children found the rate increased in nine. A bed calorimeter was used. Bowman and Fry (1925) in 15 patients and Nielson (1925) in 18 patients obtained average readings of minus 2 and minus 10 per cent respectively. DeCrimis (1925) did extensive respiratory experiments on 7 patients but did not calculate their basal metabolic rates. Jirsch (1927) in 40 women found positive values "in the majority." Jennox and Wright (1928) have measured the basal metabolic rate of 130 patients. Of these 68 per cent were

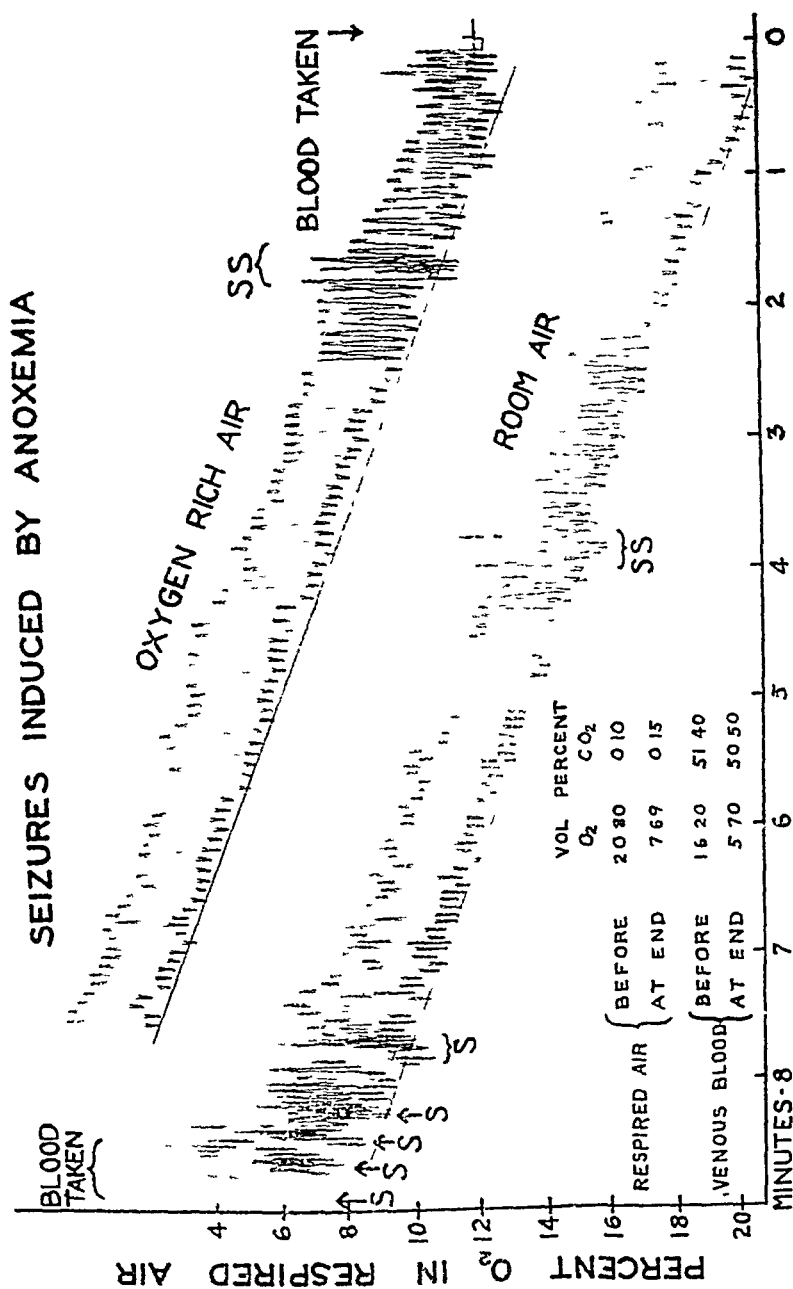


FIG 5 SEIZURES INDUCED IN PATIENT D T BY ANOXEMIA

Graphic record of respirations made by use of Benedict-Roth basal metabolism apparatus. The ordinate which applies only to the lower curve represents the percentage of oxygen in the respired air. The abscissa marks minutes. The chart reads from right to left. In the upper record, the apparatus was filled with oxygen rich air, in the lower record with room air. SS marks spontaneous seizures, S marks seizures resulting from anoxemia. There was no measurable decrease in the consumption of oxygen before either of these two types of seizures. Chart is one-half the size of the original.

between plus or minus 10 per cent, the strict limits of normal. Twenty-three per cent were below minus 10 per cent, and 12 per cent were below minus 15 per cent. The average reading for the whole group was minus 3 per cent.

From these preliminary data one may say that the majority of adult patients with convulsions, have either a normal or a reduced rate of oxygen consumption. In our series, patients with reduced rates did not show clinical evidence of myxedema. Some patients had evidence of hypopituitarism, some had faulty body mechanics, some seemed to correspond to the low rate, symptomless group which workers in various metabolism clinics have encountered. Concerning fluctuations from time to time in a basal metabolism of the same patient, Frisch (1927) obtained differences as great as 40 per cent. He did not present control observations to show that these variations were not due to technical difficulties. In a number of fasting patients we have made daily measurements of the oxygen consumption, charting them against the frequency of seizures (see fig 12). Though there was no constant correlation between the two, in general both oxygen consumption and seizures were reduced during fasting. In several instances we administered thyroid during fast with resulting increase in seizures. It is possible that low metabolic rates in patients are a mechanism of defense.

The foregoing observations have to do with the oxygen consumption in interparoxysmal periods. Long ago the theory was advanced that the immediate cause of seizures was a decrease in the oxidative processes within the body. DeCrisis (1925) stated that he had found a decrease in oxygen consumption and carbon dioxide production immediately before a seizure, but did not present convincing data. Arnoldi and Ferber (1923) in one patient observed a decrease in the amount of oxygen consumed before a convulsion. In view of the methods used and the variability in metabolic rates in healthy subjects from time to time, these isolated observations are not significant. We have graphic records of the oxygen consumption of patients having petit mal or mild convulsive seizures (fig 5). They do not show significant change in the amount of oxygen used, either before or after the spell, except in instances in which muscular work was involved, when the consumption was increased.



We must remember that measurements of the basal metabolic rate record the oxygen consumption of the whole body, and changes in the rate of oxidation in nervous tissues alone would probably not make a measurable difference. These observations, therefore, do not prove that a decreased oxidation in the brain is not related to seizures. Indeed in our patients having frequent seizures daily, we have demonstrated that anoxemia may induce an attack. One of our patients is a girl who has many short, clonic seizures daily. If she breathes into a portable metabolism machine, the bell of which is filled with room air (expired  $\text{CO}_2$  being absorbed) she invariably has seizures when the oxygen content of the respired air has fallen to 8 or 9 volumes per cent. These attacks are similar to her spontaneous ones, they recur at intervals of a few seconds until oxygen is admitted into the bell, when seizures cease, not to return till the oxygen which was admitted has been consumed. Record of one such experiment is shown in figure 7. Although acute anoxemia is accompanied by alkalosis, due to the increased lung ventilation and elimination of  $\text{CO}_2$ , in these experiments alkalosis must have played but a minor part, for the records show only slight increase in the respiratory rate and, when the spells occurred, the  $\text{CO}_2$  content of the venous blood was not changed. We found that by having this patient breathe an oxygen-rich atmosphere, seizures from over-ventilation can be prevented (see fig. 8). Probably anoxemia is a factor which is effective only in patients whose seizure mechanism is equipped with a hair trigger. We failed to produce seizures by this means in several other patients whose spontaneous seizures occurred at relatively infrequent intervals.

In résumé, we may say that the decreased oxygen consumption which many patients show may be a mechanism of defense, for artificial stimulation by means of thyroid feeding often increases seizures. There seems to be no change in the rate of oxygen consumption before seizures, but if a patient having frequent seizures breathes oxygen-poor air seizure may result. Other data are given on page 229.

### *Endocrine glands*

Many physicians have attempted a correlation of seizures with abnormality in the functioning of the glands of internal secretion. Such

correlation is difficult because of the incomplete state of our knowledge concerning the clinical manifestations of disordered function of the various glands, and because of the difficulty of applying specific therapy when abnormality is found. Many of the contributions in the literature are in the form of isolated case reports.

*The thyroid gland* Apparently few careful post-mortem studies have been made of the thyroid gland in epileptics.

Buscarno (1922) described crystals representing abnormal proteins in the thyroid glands of 71 per cent of epileptic patients and 14 per cent of normals. He considers that seizures are an anaphylactic crisis, due to these proteins, and proposes thyroidectomy and the oral administration of thyroid substance. He also states (1924) that both epilepsy and goiter are most frequent near the sea. The prophylaxis of the two conditions is the same. Various French authors have described flattening of the epithelial cells, whereas German investigators have found no histological changes. There is considerable difference of opinion concerning the frequency of convulsions in states of hypothyroidism and hyperthyroidism. Serejski (1926) has recently reviewed the literature and adds 4 cases in which patients with convulsions had signs of hyperthyroidism. Basal metabolic rates were not measured. In our experience the coexistence of hyperthyroidism and epilepsy is rare. In fact, we have seen only one such patient, a woman with well marked signs of exophthalmic goiter and a basal metabolic rate 37 per cent above the average normal.

Evidence that seizures may be associated with hypofunction of the thyroid gland is more abundant. As we have mentioned above, about one-fourth of the 130 patients examined by Lennox and Wright (1928) consumed an abnormally small amount of oxygen, per unit of body surface. It is not certain, however, that this is due to hypofunction of the thyroid, for these patients were not myxedematous. They found by chance that mothers of two of the low rate patients had definite myxedema. In our experience, raising the basal metabolic rate of patients to the normal level by means of thyroid gland was not accompanied by a decrease in the frequency of seizures. Bolten (1914) considered that essential autointoxication produced

tract, with the formation of intermediary toxic products of metabolism. Such intoxication, he believed, was due to hypofunction of the thyroid and parathyroid glands. Treatment should consist in the rectal administration of these glands. Such treatment (1915) of a "large group" of patients during the previous 10 years had resulted in two patients being free of seizures for 10 years and 20 being free for a period of from 3 to 10 months, hardly a striking result. The reason for administering fresh glands by rectum rather than by mouth is not given. Gordon (1908) in 6 patients and Demole (1924) in one noted improvement following the administration of thyroid. The patients of Prior and Jones (1918) and of Kafka (1923) were made worse. Concerning animal experimentations, Fischer and Fischer (1914) tried the effect of amyl nitrite convulsions on two animals previously thyroidectomized. Because these animals showed marked convulsions, they concluded that loss of thyroid intensifies seizures. The meagerness of the material and the fact that the experiments were not controlled make this evidence useless. Uyematsu and Cobb (1922) found that susceptibility of rabbits to induced convulsions was apparently increased by thyroidectomy and decreased by thyroxin. Elsberg and Stookey (1923) confirmed the effect of thyroidectomy. Hammet (1926) has made the interesting observation that following the removal of the thyroid and parathyroid glands in animals there is an abnormally low water content of the brain and spinal cord.

Except in rare instances there is no evidence that there is abnormality in the function of the thyroid gland in epilepsy, or that the administration of thyroid gland is of value.

*Parathyroid glands and tetany.* Because of the analogy with the convulsive phenomena of tetany, the question of the function of the parathyroid glands in persons with unexplained convulsions is an important one. Evidence concerning the parathyroid in epilepsy may be obtained at necropsy, from measurements of calcium and phosphate in blood and spinal fluid, from measurements of the excitability of nerves, from data concerning the coexistence of tetany and epilepsy, and from observations concerning the effect in epilepsy of measures which are effective in the treatment of tetany.

Reports concerning the condition of the parathyroid glands at

necropsy are meager Volland (1910) in 24 cases found abnormality of a parathyroid in one

Evidence concerning the concentration of calcium and of phosphates in the body fluids in epilepsy is reviewed under acid-base relations Little evidence of abnormality has been found Bisgaard (1925) saw a common factor in the disproportionate excretion of ammonia which patients with tetany and epilepsy exhibit In both conditions the administration of parathyroid glands tended to diminish this abnormality

Investigations have been made to determine whether epileptics present alterations in the excitability of nerves, as measured by the reaction to the galvanic current Frisch and Walter (1922) in a few epileptic patients tested daily, found an increase of nerve irritability to galvanic current as the day of seizure approached Romer (1923) in 250 patients demonstrated increased excitability of nerves in 16 per cent A small number of these gave a history of spasmophilia in childhood Hopmann (1925) in 4 patients tested excitability of muscle before and after seizures without finding any change

As to whether tetany may pass into epilepsy, or whether the two conditions may coexist, there is a wide difference of opinion

Redlich (1911) in a 36 page article, gave a complete review of the cases in which there has been coexistence of tetany and epilepsy Perhaps the clearest association is seen in the group in which parathyroid glands had been removed surgically Although symptoms of tetany appeared immediately, in many instances generalized convulsions did not begin for months afterwards An interesting observation is the one that many epileptic patients have Chvostek's sign without other evidence of tetany Fuchs (1917) recited instances in which soldiers who ate bread made from spoiled corn containing ergot had tetany and generalized convulsions Both ceased when this bread was eliminated from the diet Curschmann (1918) added a few case reports of patients presenting evidence of both tetany and epilepsy who were relieved by small amounts of  $\text{CaCl}_2$  Fischer and Leyser (1922) in a 40 page review of the literature which contains no references presented arguments for a common basis of tetany and epilepsy in a disturbance of endocrine function Thom (1924) traced

the after history of 29 children who, on hospital entrance, were diagnosed as having spasmophilia. Sixteen of these later became subject to recurring convulsions or deteriorated mentally. Powers (1925) told of an infant of 7 weeks with generalized convulsions apparently the result of birth injury, whose blood chemistry, electrical reactions and response to treatment made the diagnosis of tetany certain. Kalischer (1926) and Sachs (1926) believe tetany and epilepsy are not related.

Many of the reports concerning therapeutic results from the oral administration of calcium are without significance because of the limited number of patients treated or because of the small amounts of calcium given. Obregia and Urechia (1914) injected 5 to 10 cc of 10 per cent solution of  $\text{CaCl}_2$  into the subarachnoid space of 86 patients. The injections were accompanied by reaction, temporary paralysis of legs and some decrease in seizures. Data are not given. Small amounts of calcium chloride were injected intravenously by Petzetakis (1925) in two patients with good effect and by Klein and Forcione (1927) in 14 patients with bad effect. Frugoni and associates (1926) believed they cured a man suffering from tetany and epilepsy by implantation of parathyroid glands. Massaglia (1924) gave insulin to 4 dogs in which 3 to 4 parathyroid glands had been removed. One animal died in convulsion and 2 others had tetanic spasms of the hind legs. Four normal dogs given insulin as controls suffered no symptoms. He considers it possible that some forms of epilepsy may be the result of decreased parathyroid and increased pancreas function.

With our present ability to mobilize calcium by means of subcutaneous injection of the parathyroid hormone prepared by Collip, one is in a position to determine the influence of changes in calcium content of the blood on seizures. Sherrill and Copp (1926) speak of one case in which there was freedom from convulsions when serum calcium was kept high by this means. Madson (1927) saw reduction of seizures in 3 of 5 epileptics treated with Collip's parathyroid. However, he gave the preparation by mouth, a method which is almost without effect, and he made no measurements of blood calcium. One of our patients who had certain evidence of tetany was given in 12 days 500 units of parathyroid hormone intravenously, together with

large amounts of calcium lactate by mouth, without affecting either the seizures, the Chvostek's sign, or the concentration of serum calcium

In résumé we may say that only in the exceptional patient is there evidence of coexistence of tetany and epilepsy. The calcium content of body fluids in epileptics is normal and patients do not receive benefit from administration of calcium or parathyroid gland. On the other hand, there is some common ground for these two conditions because procedures which will precipitate tetanic muscular contractions in persons predisposed to tetany will also precipitate convulsive seizures in patients with epilepsy. Collip (1926) has reviewed the conditions which will induce tetany. Some of these are: Any salt which will precipitate calcium in the tissues and body fluids, intravenous injections of large amounts of sodium chloride or sodium bicarbonate, forced ventilation of the lungs, and conditions of anoxemia. Collip states that at least three factors influence the production of experimental tetany, namely, tissue anoxemia, disturbance in ionic equilibrium and pH. As we show in other sections of this paper, these three factors may also precipitate convulsions in epileptic patients. They increase the irritability of nerve tissue, and in this way bear a fundamental relationship to both tetany and epilepsy, possibly there is also a relationship to other conditions in which there is potential hyper-excitability of nervous tissue. In addition, certain conditions which improve tetany, as administration of acid-forming salts and breathing of  $\text{CO}_2$  (Swingle, Wenner, and Stanley, 1927) may favorably influence epileptic seizures. The study of this problem would seem to offer a fruitful field for future research.

*Adrenal gland* The adrenal glands are often accused of being implicated in the mechanism by which seizures are produced. The anatomical findings are not impressive. Volland (1910) in 40 autopsies found abnormality of an adrenal gland (tuberculosis) once. In 359 autopsies performed at the Craig Colony 8 per cent showed abnormality, usually hypertrophy of the adrenals. Popca and Eustatziu (1925) found almost complete absence of lipid material in the adrenal cortex of two patients who died in status. They suggest that this material was exhausted in combating the toxemia produced by the muscular exertion of seizures.

That excess secretion of the adrenals may, on occasion, precipitate a seizure is suggested by the fact that seizures sometimes follow the subcutaneous injection of adrenalin. Benedek (1918) discussed the possible influence of the adrenal glands and gave (1923) the results of adrenalin injections in patients. Seven of the 19 epileptic patients who received from 1 to 1.5 cc of tonogen had typical seizures within one-half hour after the injection. In three patients in whom there was no effect, injection of tonogen and thyroid gland resulted in a seizure in one. Injection of pilocarpin apparently stopped a seizure in one case. He suggested that adrenalin acts by altering the blood supply of the brain. Bertolani (1926) injected adrenalin up to 3 cc. in a group of 48 patients. Three of these had seizures. He considered the results negative. Freidman and Lennox (unpublished data) have injected adrenalin in patients on 70 occasions, precipitating a seizure only once. Amounts of adrenalin injected were many times larger than the amounts secreted by the adrenals.

Fischer (H.) and Fischer (J.) (1914) started a wave of interest in the adrenal glands in epilepsy through certain animal experiments. They produced convulsions in 22 rabbits by causing them to inhale 8 to 12 drops of amyl nitrite. On autopsy the adrenal glands showed a lack of chromaffin staining material. They suggested that hyperfunction of adrenal and parathyroid glands increased the severity of seizures. Fischer (H.) (1920-1921) continued the observations begun in 1914. He gives protocols of 4 experiments in which an adrenal gland was removed. Inhalation of 12 drops of amyl nitrite before the operation would produce a convulsion, whereas 15 drops after the operation would not. Fischer believed that the convulsive capacity of the animals was diminished by the adrenalectomy. From these experiments, he concluded that the tonus of striated muscle is increased by adrenalin and decreased by adrenalectomy, and that in the latter condition there is a heightened threshold for convulsions. Apparently there were no control experiments to determine whether anesthetization and the severe operative procedure involved in adrenalectomy might in themselves result in a decreased response to the convulsant drug. Wertheimer and Dubois (1922) criticized the experiments because Fischer used rabbits, animals which are not subject to convulsions from cortical stimulation. These authors used dogs and

found that removal of the adrenals did not hinder convulsions produced by intravenous injection of strychnine. Specht (1922) repeated Fischer's experiments, using tetanus toxin instead of amyl nitrite and found no difference in reaction between operated and control animals. In other experiments in which they used amyl nitrite with 130 guinea pigs and rabbits, they were not able to stop convulsions by extirpation of a gland. We need not follow the heated discussion between authors which ensued.

On the basis of this inconclusive animal work, a number of German surgeons repeated the experiment in patients. Brüning (1920) performed one-sided adrenalectomy on 9 patients, two of whom were freed of seizures. Favorable results were reported by Sándor (1921) in four cases, Fischer (H.) (1922) in one case, and Klieneberger (1922) in one case in which an adrenal was removed, and 12 cases in which it was irradiated. The negative votes, however, soon outweighed the positive. Peiper (1921) in 7 cases, Steinthall (1921) in 7 cases, Cordua (1921) in 1 case, Sultan (1922) in 5 cases, Heymann (1922) and Engelbrecht (1922) in 10 cases, Jung, Géza and Szórády (1922) in 9 cases, Kutscha and Lissberg (1923) in 11 cases, Küttner and Wollenberg (1923) in 4 cases, and Schonfeld (1923) in 10 cases, reported unfavorable results. Little is said concerning operative mortality. Chian (1922) removed an adrenal gland from a patient who later developed symptoms of Addison's disease.

Neither the inconclusive experimental studies nor the negative effects of adrenalectomy prove that the adrenal glands may not play a part in the mechanism of seizures. However, if there were any great increase in adrenal secretion before the onset of seizures, the heart rate, blood pressure and blood sugar would show an increase, which they do not. During the seizure, as in any muscular effort, the adrenal output must be greatly increased.

*Pituitary gland* Cushing's work (1912) suggests that the internal secretion of the pituitary gland enters the spinal fluid, bathes the cortex of the brain and thereby reduces its excitability. It is possible, therefore, that a decrease in the secretion of the pituitary or adhesions of the pia preventing access of the fluid to the brain, would contribute to the production of seizures. Furthermore, it is well known that tu-



mors of the pituitary gland are often associated with convulsions, as was noted, for example, in 18 of 98 cases in Cushing's series

The data from autopsy material are limited. Munson and Shaw (1914) found no constant changes of the pituitary in a series of 22 autopsies. Of 100 glands examined at the Craig Colony, the average weight was 544 mgm or 10 per cent below normal

In the living patient, indirect information concerning the size of the pituitary gland may sometimes be gained through examination of visual fields, measurement of intracranial pressure, and x-ray of the sella turcica. Evidence concerning disturbed function is gained through study of the body type, distribution of hair, the type of blood sugar curve, presence of polyuria, etc. There are a number of case reports in the literature in which individual patients or small groups of patients with convulsions gave evidence of abnormality of the pituitary gland. In some of these there was improvement under administration of pituitary extract. Redlich (1914) cited two patients in whom clinical signs were unusually well marked. Loughlin (1915) told of a girl of 16 who gained 50 pounds in weight in one year and whose seizures were less severe while she took pituitary extract. Rubenson (1917) described a boy whose diabetes insipidus and seizures improved following the injection of pituitrin. Tucker (1919) in 200 patients with epilepsy thought he found evidence of pituitary disturbance in nearly one-third, 28 were distinctly endocrinopathic and were treated with gland substance, 5 had been free of seizures for 3 years. The following authors give case reports concerning the stated number of patients. Prior (1921) and Blumgarten (1921) 5, Malamud (1922) one, Lowenstein (1922) 16, and Lissner and Nixon (1923) 6. Some of these patients improved while under treatment with pituitary gland.

Only a small proportion of patients with convulsions show clear-cut evidence of pituitary gland disturbance antedating the onset of convulsions. In such patients seizures seem to bear a close relationship to disturbance of the gland. This indicates that the intimate anatomical relationship of the pituitary to the brain may have a physiological significance.

*Thymus gland* Volland (1910) in post-mortem examinations of 100 epileptic patients found a persistent thymus in 20. In 423 examinations at the Craig Colony a persistent thymus was reported in only three, 0.7 per cent. Even case reports are few. Prior and Jones (1918) stated that 4 of their patients were better while eating thymus gland. Browning (1920) and Lennox and Cobb (unpublished data) each treated a patient who gave evidence of persistent thymus. Our patient was an 18 year old girl who presented no physical abnormality other than slight dysmenorrhea, obesity, and decrease in basal metabolic rate. She was studied very thoroughly, underwent two fasts without benefit, and was later found dead in bed. Autopsy showed no cause for death or seizures other than a condition of status lymphaticus. The thymus gland weighed approximately 200 grams. The ovaries contained numerous cysts and the uterus was infantile.

*Gonads* There is little in the literature concerning the relationship of sex glands of the male to seizures. There are scattering reports of convulsions which have developed after castration but apparently seizures are not unusually common in eunuchs.

The question of the influence of the gonads in females has received more attention. This is probably because of the well-known fact that many female patients frequently have seizures near the time of menstrual periods.

The single experiment by Fischer (H) and Fischer (J) (1914) in which a pregnant rabbit had an unusually severe convulsion after administration of amyl nitrite was entirely uncontrolled. Rebattu, Mollon and Sedallian (1922) in 100 female patients thought there was relationship between seizures and menstruation in 35, of 94 patients, 8 began to menstruate late and in 6 the first menstruation was accompanied by a seizure. Winter (1923) charted seizures and menstrual periods of a patient for  $1\frac{1}{2}$  years. X-ray exposure stopped both for a three months period. Toulouse and Marchand (1913) and Marchand (1922) believe that ovarian disturbances bear no constant relationship to seizures. The case reports of van den Berg (1921), of Pichler (1923) and of D'Abundo (1923) are not convincing. Reports concerning the effect of glandular therapy are meager, presumably because negative results do not readily find their way into the litera-

ture. A number of years ago when hysterectomy was a favorite pastime of surgeons, undoubtedly many patients were deprived of their sex organs but not their seizures. Ashe (1920) saw some improvement in 3 patients treated with ovarian substance. Everke (1923) cited 3 patients apparently cured by removal of ovaries or uterus, and Marchand and Adam (1923) one patient whose seizures began after hysterectomy. Cotte and Rebattu (1924) operated upon 2 patients but saw no beneficial results.

We believe that convulsions which occur only before or during menstruation may be most easily explained by the increased nervous irritability which many women exhibit at that time. The condition is analogous to that observed in certain parathyroidectomized female dogs, which have tetany only when in heat (Collip, 1926). A possible mechanism for such increased irritability is the increase in capillary permeability which has been observed during menstruation.

*Pancreas* The relation of the internal secretion of the pancreas to carbohydrate metabolism is so close that the question is discussed under that heading.

*Combined gland disorders.* In any clinical study of endocrine glands, the fact that there may be abnormality of more than one gland greatly complicates the problem. Concerning such polyglandular disorders, either with or without convulsions, we know little. The case reports supplied by vendors of shotgun glandular prescriptions are too prejudiced to be of value. Sserdjukoff (1925) believes that in epileptic women there is often disturbance of the ovary, thyroid, pituitary and uterus. His evidence for this view is not clear. Shou and Susman (1927) found perivascular necrosis in the various endocrine glands of 5 of the 6 cases examined.

*Summary.* There is need of a thorough, objective study of a large series of patients in order to determine more exactly the part played by the endocrine glands in epilepsy. On the basis of our present information, we can say that only a few patients having seizures present clinical evidence of endocrine abnormality. The glands which most actively stimulate metabolism are the thyroid, the adrenals, and the pancreas. In most patients increasing the intensity of the metabolic processes of the body by the administration of

the active principles of these glands tends to favor the occurrence of seizures. Abnormalities of the pituitary, when they do occur, often bear a direct relation to seizures. Though of no therapeutic importance in epilepsy, the parathyroids hold an unique relationship to epilepsy in that conditions which may precipitate tetany in parathyroidectomized animals, viz., anoxemia, disturbance in ionic balance and alkalosis, may also precipitate seizures in epileptics.

### *The blood*

Because the brain is not open for inspection during life, one might hope that examination of the blood which flows through it would reveal the presence of substances which might conceivably alter brain function. We shall discuss here only the morphology, physical properties and protein content of the blood. The chemical constituents, ferments, toxicity and bacteriology will be discussed in other sections.

*Morphology* Of the various examinations of the blood which have been made, estimations of the number and proportion of various forms of leukocytes have been most numerous. A possible reason for the popularity of the subject is the fact that observers have differed hopelessly in their findings.

The following statements illustrate the variety of conclusions reached. Krumbmiller (1898), leukocytosis during a spell with predominance of young forms and with coincident decrease in the size of the spleen to percussion, Onuff and Lograsso (1906) in 19 cases, no parallelism between seizures and leukocytosis, Morselli and Pastore (1906) in 30 cases, decrease in eosinophiles as seizure approaches, Nieuwenhuyse (1911), lymphocytosis after seizure, Müller (1913), leukocytosis both with seizures and psychic equivalents, Fackenheim (1914), leukocytosis and eosinophilia, Spangler (1916) in 100 cases, leukocytosis persisting for from 12 to 24 hours after a seizure, di Gaspero (1919), fluctuation in number of leukocytes, Wissenfeld (1921), both leukocytosis and lymphocytosis with seizure, Patterson (1923) in 128 cases presenting some manifestation of endocrine disorder, distortion of the leukocytic formula and leukocytosis, Targowla, Montassut and Krivy (1925), decrease of leukocytes in seizure. Hyperpnea in nor-

mals caused no change in leukocytic formula, while in 5 patients with epilepsy it produced inversion. Fuchs (1926) published extensive tables of the daily differential counts in 8 patients but gave no adequate discussion of the results. Wuth (1924 and 1926, a and b) found leukocytosis and eosinophilia during seizures. This list does not include ten authors whose findings are tabulated by Wuth. Apparently observers were not always careful to take into account the influence of food or of hidden infections. Different authors interpret the fluctuations observed in different ways as a reaction to a circulating toxin, as an anaphylactic phenomenon, or as a response to disturbance of the endocrine glands or of the autonomic nervous system.

Pagniez and Lieutand (1919), Pagniez (1921) and Bouché and Hustin (1921) speak of the relation of hemoclastic shock (the leucopenia of digestion) to seizures. The first named fed chocolate to a patient after meals and on two occasions in which leucopenia resulted, seizures occurred within a day. Tinel and Santenaise (1921, 1922) state that hemoclastic shock occurs only at the time of mental upset or seizure and is suppressed by luminal. Data presented are insufficient and contradictory. Thomas and Lascelles (1927) found hemoclastic crisis in 17 out of 31 patients examined.

The question of the number and proportion of the leukocytes of the blood seems of little importance. Evidently the leukocytic count and formula are essentially normal except at the time of seizures. At that time leukocytosis may occur, presumably as a result of muscular work involved in the seizure.

The number of red cells and percentage of hemoglobin in patients with epilepsy is usually normal. Apparently certain institutional groups of cases may show anemia, possibly as a result of a meat free diet. Fackenheim (1914) found hemoglobin of 50 to 60 per cent in two-thirds and from 60 to 70 per cent in one-third of 100 epileptics examined. Wuth (1922) in 40 cases found the red count between 5.7 and 2.6 millions with an average of about 3.8 millions. Hemoglobin ranged from 98 to 46 per cent with an average of about 82 per cent. Convulsions may be a symptom of polycythemia, or may occur after transfusion in pernicious anemia.

We have made hematocrit readings in 100 patients (9 cc of blood

centrifuged at 2500 revolutions per minute for 30 minutes) In this group the proportion of red cells to whole blood was as follows Average for the men 49 per cent, the highest reading being 56 per cent and the lowest 40 per cent. Average for the women 45 per cent, the highest reading being 55 per cent and the lowest 45 per cent. These are normal measurements for the method used

Burkhardt (personal communication) did blood grouping of 90 patients Of these, 5 per cent belonged to group 1, 30 per cent to group 2, 21 per cent to group 3 and 43 per cent to group 4 Group 2 was slightly smaller and group 3 larger than most. Claude, Schmiergeld and Blanchetiere (1908) found normal fragility of red cells in 13 epileptic patients

*Viscosity* Using Hess's Viscosimeter, Brown (1910) obtained 4.8 as an average value for the viscosity of the blood of 15 epileptics, 4.2 being the average value in healthy persons Meyer (1925) reported a lowering of viscosity in relation to seizures, but gave no data

We have seen no observations concerning the blood volume in epileptics

*Coagulation* Some writers have believed that seizures might be explained by an increased coagulating power of the blood, causing thrombosis or stasis in small cerebral vessels On such a supposition is based the treatment of epilepsy with injection of snake venom, a measure which is supposed to lengthen the clotting time of blood In spite of its apparent simplicity, the test of coagulation time is open to numerous errors and no importance can be attached to small differences Besta (1906) using 30 to 40 cc of blood and a complicated method, found diminished coagulating power in 37 of 45 patients examined Turner (1907) reported increased speed of coagulation With the use of Boggs' coagulometer, the following observations were obtained Austin (1910), slight increase in speed in 24 patients, Jenkin and Pendleton (1914), decreased speed in 9, Spangler (1916), increased speed in 50 of 100 patients. Tackenheim (1914) (method and number of cases not stated) reported quickened coagulation time, especially before seizures Thom (1914) using the method of Lee and White, in a group of 203 patients found a normal clotting time (3 to 8 minutes) in 92 per cent Coagulation time in

the remainder varied between 2.5 and 14 minutes Wuth (1922) in 40 patients found a narrower range, 1 to  $3\frac{1}{2}$  minutes In two patients daily tests made for 22 days varied between 1 and  $2\frac{1}{2}$  minutes Chiola (1925) (Cinffini method) in 35 cases and Choroschko (1925) (method of Sitkowski-Jegoroff) in 30 cases found quickened coagulation which was greatest on the approach of a seizure

The variety of methods used by these various observers does not permit comparison of results We accept the statement of Thom and Wuth that the coagulation time is normal The presence in the blood of amounts of calcium and of fibrinogen which are not abnormally low would indicate also that there is nothing seriously at fault in the clotting ability of the blood.

*Sedimentation* Wuth (1922) found increased speed of sedimentation of red cells in many of the 40 cases examined Readings at the end of an hour varied between 28 and 1, with an average value of about 4 (method of Von Plaut). The speed of sedimentation did not vary with the number of leukocytes or erythrocytes Lowenberg (1923) in 7 of 14 patients obtained an increased rate and found increased speed in sedimentation following seizure in one patient Hughes and Lennox (unpublished data) found increased rates in about one-third of 72 patients examined The increased speed of sedimentation agrees with the increased fibrin content of the blood in patients observed by Lennox and Allen (1928)

*Flocculation.* Georgi (1924-1925) stated that in a group of 44 patients he measured speed of sedimentation, viscosity of plasma, refraction, coagulation, alkali reserve, calcium and the colloidal stability of the blood The only data presented are in a table showing the results of several flocculation and sedimentation tests, and demonstrating an increased degree of flocculation of the plasma of epileptics. As the discussion is principally concerned with changes which take place during hyperpnea, the papers will be discussed under that heading.

*Fibrinogen* Fibrinogen is an important factor in the process of clotting Decrease of blood fibrinogen occurs in serious liver damage and increase occurs in conditions of tissue injury and inflammation, whether the latter is septic or aseptic in origin Of the plasma pro-

teins, it is the one which can be most readily and accurately measured Besta (1909) examined 45 patients, all but 8 of whom showed decrease in fibrin ferment Dienst (1922) believes that in conditions of debility or poor circulation there is deficient formation of anti-thrombin, and that the increased concentration of thrombin which results is the cause of convulsions or of eclampsia He says the content of anti-thrombin in the liver is high in pregnancy but not in eclampsia The injection of fibrin ferment in rabbits produces convulsions through spasm of capillary vessels Apparently, the only laboratory observation on which this theory is based, so far as epilepsy is concerned, is the finding of less than one-half of the normal amount of anti-thrombin in the blood of epileptic patients Dienst (1926) further believes that abnormally increased amounts of thrombin in the blood have a toxic vasoconstrictor action, secondary to which there is an increase in fibrinogen He speaks of thrombin as the sheet lightning and thunder and fibrinogen as the lightning stroke in the eclampsia tempest Foster (1924) states that toxemia of pregnancy is associated with an increase of blood fibrinogen whereas nephritis complicating pregnancy is not

Lennox and Allen (1928) have measured the fibrinogen content of the blood in 100 patients with epilepsy In 34 per cent of both men and women, measurements were above the upper limits of normal In all but 7 of these patients the presence of any manifest infection was ruled out by normal temperatures and often by normal white counts High values were not found in patients having the most frequent or severe convulsions Whether this increase is an evidence of an irritative process in the liver or is due to an increased katabolism of body tissue is unknown In one of our patients from whom blood was taken before and after seizures, the fibrinogen content of the blood did not vary

*Serum albumen* Meyer and Bruhl (1922), Bruhl (1923) and Meyer (1925) measured serum albumen in a group of 16 patients The chief abnormality found was a discrepancy in measurements obtained by the refractometric and Kjeldahl methods (the former being higher) They concluded that the refractive property of serum albumen in these patients was affected Data are not presented, observations are too



few to be conclusive, and we know that measurements by refractometric and Kjeldahl methods normally show a discrepancy. Wuth (1922), using the Zeiss dipping refractometer, found that values of serum albumen in 40 patients varied between 10.23 and 7.24 with an average of about 8.3. He thought the few high values obtained were due possibly to increase of blood pressure during seizures. Daily measurements made of two patients for three weeks showed little daily fluctuation. Subsequently (1926, a) he found that serum albumen was somewhat increased after seizures. The serum-globulin ratio was normal in 23 patients. Frisch and Fried (1926), using a gravimetric method, found a high ratio of albumen to globulin in five patients having frequent seizures. In a small group of patients, using Wu's colorimetric method, we have obtained essentially normal values.

*Wassermann reaction* Many practitioners consider that they have fulfilled their duty towards their epileptic patients, so far as the laboratory side of medicine is concerned, if they have a blood Wassermann test performed. Some French authors consider syphilis as an important cause of epilepsy.

Toporkov (1925) states that 140 patients were improved with anti-syphilitic treatment. He does not say whether or not these patients gave any clinical evidence of syphilis. In this country the coincidence of epilepsy and syphilis is surprisingly small. Novick (1921) found that 2.2 per cent of 231 patients with epilepsy had syphilis. Shanahan, Munson and Shaw (1916) in routine Wassermann tests of 1473 patients obtained 1.5 per cent positive reactions. Of 305 brains examined at autopsy, gumma was found in two. Of 4100 patients examined clinically, 3.4 per cent were found to have syphilis or were suspected of having it. This is probably a smaller proportion than is found in the population at large.

*Summary.* Concerning the morphology, the physical properties, and the Wassermann reaction of the blood, there is no evidence of consistent abnormalities which might be thought of as contributing to the production of seizures. The presence of increased fibrinogen and speed of sedimentation of red cells in a minority of patients may be evidence of an unusual degree of tissue destruction in these patients.

*Spinal fluid*

Because the spinal fluid is in such intimate contact with the brain, one might hope that study of the spinal fluid of persons with epilepsy would reveal some abnormality. Most workers, however, state that the spinal fluid in epilepsy is normal. Concerning any such statement, however, one must inquire as to the completeness of the examinations made. We are interested not only in the character and constituents of the fluid itself, but also in its volume and pressure. Chemistry of the fluid will be discussed later.

*Pressure* In spite of the importance as well as the simplicity of spinal fluid pressure readings, most clinicians either disregard this feature of the examination, or are content with observing the apparent force with which the fluid is ejected from the needle, a worthless observation. For this reason, the evidence which we have is fragmentary and contradictory.

Nawratzki and Arndt (1899) found normal pressure in 3 cases. Redlich and Potzl (1910) measured the pressure in 39 cases, in which x-ray suggested abnormality. Five of these showed constantly high pressure—from 200 to 400 mm of water. Larkin (1919) in 59 cases found pressure above normal in 31 per cent, and below normal in 15 per cent. This statement is without meaning as normal values were not defined. Wittengenstein (1923) in 10 patients found pressures between 105 and 200, both before and after seizures. Patterson and Levi (1926) in 50 patients in the sitting position, obtained pressures between 6 and 38 mm of mercury. Lenche (1920, 1921 and 1922) in contradiction to the trend of evidence already presented, believes that hypotension may be a factor in inducing seizures, and suggests the use of intravenous injection of distilled water or of pituitrin or even ligation of the inferior longitudinal sinus. Perusal of Lenche's articles fails to show any data concerning measurements of spinal fluid pressures in a series of cases. His opinion, therefore, may be dismissed without discussion. Tilmann (1926) states that he has performed lumbar puncture in from five to six hundred patients with epilepsy. Pressure was high in 75 per cent and low in 10 per cent. Here again the author fails to define his limits of normal or to present any detailed data concerning measurements.

We have made records of the spinal fluid pressure measurements in more than 200 unselected patients in whom seizures were the presenting symptom. In nearly 20 per cent of the patients, the initial pressure was above 200 millimeters of spinal fluid, the upper limit of normal. Because duration of symptoms in these cases did not parallel the increase in pressure, it would seem that such increase was not the result of seizures. Six of our patients with increased pressure were found to have brain tumor at operation or autopsy.

Evidence of chronic increase in intracranial pressure is furnished also by x-rays of the skull. We have seen no report of the correlation of such evidence with that obtained by spinal puncture.

All observers are agreed that during the seizure itself, spinal fluid pressure is greatly increased.

Nawratzki and Arndt (1899) observed three cases, in one of whom pressure rose to 870 mm. Redlich and Potzl (1910) observed a rise to 450 mm. in one case. Dalma (1925) produced seizures in three patients by means of hyperventilation and observed pressure as high as 500 mm. In one of our patients pressure during a convulsion rose to 700 mm. The spinal canal was drained. Twenty-four hours later the pressure during convulsion rose to only 100 mm. Increase in pressure did not precede the seizure. In several instances we observed no change in spinal fluid pressure during petit mal. Ebaugh and Stevenson (1920) made continuous graphic record of relative changes in intracranial pressure by means of a tambour applied to the head of a patient with a large skull defect. Variations with relation to seizures and the use of hypertonic and hypotonic solutions were recorded.

Increased pressure in seizures is secondary to the apnea and the increase in venous pressure which occurs during the tonic phase of convulsions. The height to which pressure rises depends also on the arterial blood pressure and the volume of fluid in the cerebral ventricles. The general correspondence between pressure of the cerebrospinal fluid and venous and arterial blood during convulsions in animals has been shown by MacDonald and Cobb (1923). The marked phenomena observed by Foerster (1926) and others in the exposed brain at operation would naturally be associated with changes

in spinal fluid pressure, the possible mechanism of which has been discussed under cerebral circulation

*Effect of modifying spinal fluid pressure* If there is abnormality in the pressure of spinal fluid in patients, it is important to know whether modification of such pressure has favorable influence in the incidence of seizures. A number of writers have reported beneficial results from spinal fluid drainage in status

Hodskins and Morton (1905) seem to have been the first to advocate this. Others are Allen (1908), Pichenot and Castin (1907), Tissot (1908), Castin (1910), Heidelberg (1912), Gluschkow (1912) and Toulouse and Marchand (1922). Bossert (1918) recorded the death of one patient after lumbar puncture, but the presence of fever, vomiting, and headache suggests that the child may have had meningitis. Most of the foregoing favorable observations have been based on one or a few cases only. Prior and Edwards (1926) had a recovery rate of 95 per cent in a series of 53 patients with status treated by spinal fluid drainage.

The treatment of patients not in status by spinal drainage has received little favorable comment. Tilmann (1926) thought there was relief for 4 of his 65 patients who had frequent lumbar punctures and, that trephining the skull usually resulted in improvement, though only rarely in cure. Leriche's suggestions for increasing pressure have nothing to commend them. We have performed spinal drainage in a number of patients without benefit to them. The pressure of spinal fluid may be reduced by the intravenous injection of a hypertonic solution. Duschak (1919) injected 10 patients with 15-20 cc of a 5 per cent solution of magnesium sulphate with good results. Such treatment has been used in eclampsia.

Wolff (personal communication) has found that an increase in intracranial pressure above arterial pressure will result in convulsions in animals. Also there is some evidence that slight increase causes increased susceptibility to convulsions which are artificially induced. Elsberg and Pike (1926) altered intracranial pressure in cats by intravenous injection of hypertonic solution of sodium chloride or glucose (7 experiments) and of distilled water (6 experiments). In

the former experiments, when pressure was presumably reduced, it took three times as large a dose of the absinthe to produce a convulsion, as in the latter experiments when pressure was presumably increased. It is, of course, possible that factors other than increase in pressure were operative here. The presence of edema may be the essential consideration.

Certainly actions causing temporary elevation of intracranial pressure in patients (straining, coughing, etc.) are not associated with increased frequency of seizures. Dalma (1925) maintained jugular compression in 35 patients for as long as 5 hours without thereby inducing a seizure. As Redlich and Potzl (1910) pointed out, seizures in patients with brain tumor may be more frequent in the early stages when the increase in pressure is relatively small. In the patients which we have examined, those with high spinal fluid pressure readings were not as a rule the ones having the most frequent or severe seizures.

*Volume of fluid* Measurements of the pressure of spinal fluid before and after the withdrawal of varying amounts, gives some indication of the volume of fluid present, and, therefore, of the size of the subarachnoid space and ventricles. This, in turn, may indicate the presence of tumor compressing the ventricles or of hydrocephalus. We have made such fractional measurements in more than 100 patients with epilepsy. Though these data have not yet been checked against similar data from non-epileptic patients, many of our subjects give evidence of an abnormally large reservoir of cerebrospinal fluid. Computation on the basis of Ayala's quotient has not proven useful because we find that the quotient varies with the amount of fluid withdrawn.

*Morphology* The leukocytes in the cerebrospinal fluid are ordinarily normal in number. Larkin (1919) in 143 cases found increase in only one patient. Patterson and Levi (1926) in 50 cases found more than 5 cells in 22 per cent. Of nearly 200 examinations which we have made, only 9 per cent of the fluids had more than 5 cells per cubic millimeter. A considerable increase in cells during status has been observed in single cases by Pappenheim (1917) and Baylack, Bize and Stillmunkes (1923).

*Permeability of meninges.* Redlich, Potzl and Hess (1910) found no difference between epileptic and non-epileptic subjects in the readi-

ness with which ingested substances, such as methylene blue, sodium salicylate, bromin and acetone appeared in the spinal fluid

*Physical properties* Few observations have been reported Thabuis and Barbé (1913) found viscosity from 1 210 to 1 232 in 10 cases Cryoscopy was between 0 53 and 0 61 with an average of 0 57 These are normal values They found density slightly increased Eckel (1924) measured the electrical conductivity of the spinal fluid of 100 patients Values ranged from 0 01575 to 0 01423, the average being 0 014978 These are essentially normal values Jones (1926) found a high refractive index, 1 3385, in a six months baby The child, however, had pneumonia as the cause of convulsions Levinson and Serby (1926) measured the refractometric and viscosimetric indexes in 11 patients Measurements were between 1 33493 and 1 33517, a normal range

*Colloidal reaction* Authors have theorized that the mechanism of seizures may be related to changes in the colloidal reactions of tissue cells If this were so, one might anticipate abnormal reactions to colloidal gold on the part of spinal fluid Larkin (1919) in 114 cases found curves rising to a height of two in 46 per cent and of three in 7 per cent Patterson and Levi (1926) in 50 fluids found abnormal curves in 91 per cent, almost all of these being characteristic of the curve of cerebrospinal syphilis Presumably the technical difficulties of which they speak account for these unusual results In nearly 200 fluids collected by us, the curves reached a height of two in 6 per cent and a height of three in 3 per cent In other words, 91 per cent were entirely normal, and none was distinctly abnormal

*Total protein* The commonly used tests for albumen and globulin are of little use in measuring slight increases in protein material in the spinal fluid

Thabuis and Barbé (1913) found normal amounts of albumen in the spinal fluid of 6 patients Fremont-Smith and Ayer (1924) in 17 patients and Osnato and Killian (1927) in 49 found many with increased amounts of total protein Lennox and Allen (unpublished data) have collected a series of 250 fluids Most of these measurements are shown in the accompanying chart (fig 6) Nineteen per cent are above the extreme upper limit of normal—50 mgm Except in one or two instances there was no correlation between high total

protein and increased pressure of the spinal fluid. The fact that high values were found most frequently in patients with a short history may indicate a bad prognosis for life. Increased concentrations of protein without increased cell count or other evidence of inflammation often indicates the presence of a tumor in the vicinity of a ventricle Six

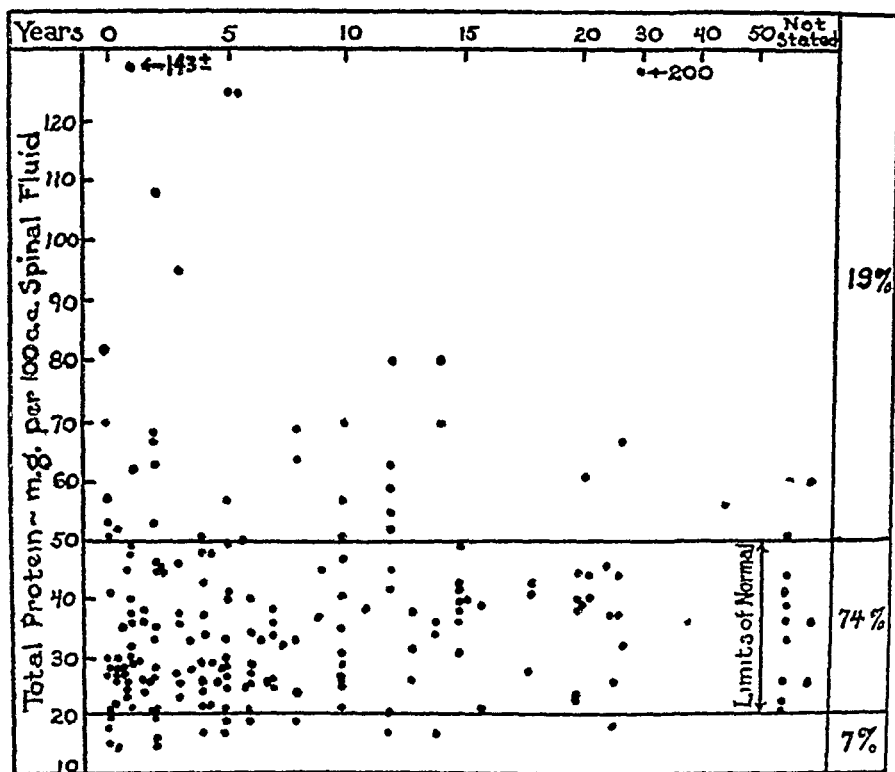


FIG 6 MEASUREMENTS OF THE CONCENTRATION OF TOTAL PROTEIN IN THE SPINAL FLUID OF 200 PATIENTS WITH SEIZURES

The ordinate represents milligrams of total protein per 100 cc. of spinal fluid (method of Ayer and Dennis). Abscissa represents the number of years in which seizures have been present. Nineteen per cent of the measurements are above and seven per cent are below the limits of normal. Values are not higher in patients whose symptoms have been present for the longest time.

of these patients had brain tumor which had not been diagnosed previously. In the others there was no evidence of tumor. The significance of the high values in these patients has not been determined.

*Wassermann reaction.* Although syphilis of the central nervous system must always be considered in patients with fits, the proportion of patients who give evidence of this condition is small. In our

series of 165 spinal fluids, 2 per cent had a positive Wassermann reaction. One of these patients had frequent daily petit mal attacks that disappeared while antisyphilitic treatment was given, and reappeared after treatment was stopped.

*Summary* Summing up the evidence with regard to spinal fluid pressures, a certain proportion of patients having convulsions without evident cause, perhaps 20 per cent, have an abnormally high pressure. In a small number this may be evidence of intracranial tumor, the cause in others is not evident. There is little clinical evidence that abnormal pressure in itself induces seizures or that reduction of pressure alleviates symptoms, except in the condition of status when spinal drainage is often of distinct benefit. Careful, fractional measurements of pressure give evidence of dilatation of the ventricles in a small proportion of patients.

Only rarely does examination of the spinal fluid give evidence of syphilis. In about one-fifth of the patients the content of total protein is above normal. Examination of patients with epilepsy by means of lumbar puncture reveals some abnormality in more than one-half. The proportion in which the abnormality is related in a causal way to the seizures is, of course, very much less.

### *Urine*

Measurements of body weight and of the volume of urine require no modern laboratory methods. For many years writers have remarked on fluctuations of the weight of patients with relation to their seizures, and on the polyuria which frequently succeeds a convulsion. Allers (1912) refers to some 20 odd articles on the subject. Even in such a seemingly simple observation, there is no unanimity of opinion. Also many of the published observations fail to indicate that due care was taken to control the factors of food and fluid intake. Féré (1890) concluded that the polyuria observed after seizures represented a variation in the vasomotor activity of renal vessels. The more modern view sees in polyuria the need for increased elimination of acid substances produced by the muscular work of the convulsion.

The fact that convulsions sometimes occur in eclampsia and nephritis raises the question concerning the functional efficiency of the kidneys in persons with epilepsy. The few patients whose ability



to excrete phenolsulphonephthalein we have measured, have proved normal in this respect. The post paroxysmal albuminuria of which older authors speak is apparently the result of the seizure. In our experience the finding of albuminuria, except following seizures, or of high non-protein nitrogen in the blood, is rare. It is rather surprising, therefore, that of 359 autopsies at the Craig Colony, macroscopic evidence of nephritis was reported in 23 per cent, and in 259 by Lind (1926), 75 per cent had "tough" kidneys. Apparently in neither case was microscopic examination made.

In an effort to detect abnormalities of metabolism in persons with epilepsy, a large amount of work has been done in measuring the chemical constituents of the urine. These older observations can now be combined with more recent chemical studies of the body fluids. We shall, therefore, discuss urinary chemical findings in sections dealing with the metabolism of food substances and the acid-base relationships of the body. Urinary ferments and toxins also will be discussed elsewhere.

### *Bacteriology of blood and feces*

This phase of the study illustrates beautifully the pitfalls in the path of "the will to find." Bra (1902) isolated an organism from the blood of 70 out of 100 cases of epilepsy at the time of seizures. Various searchers failed to confirm these results. Not knowing of this, Reed (1915, 1916a) decided that epilepsy must be due to an infection by a specific organism. Blood cultures from his cases, however, were reported as sterile. After changing bacteriologists he received reports of a spore bearing bacillus (1916, b and d) in the blood of 168 out of 211 cases of epilepsy examined. Cultures from constipated but non-epileptic patients were sterile, and the organism when injected intravenously in rabbits produced convulsions. Koch's postulates were satisfied, and the medical world was informed that at last "Bacillus epilepticus" was found. Although these findings were confirmed by Terhune (1916), negative results were quickly reported by Caro and Thom (1916) in 70 cases, MacDonald and Edward (1916) in 9 cases, Wherry and Olver (1916) in 6 cases, Munson (1917) in 130 cases, and later by Reed (1917) himself. In the course of the controversy, Reed made this revealing statement "I, like other clinicians, must

accept and be guided by the technical findings of pathologists and bacteriologists, but they must be the findings of something, not of nothing" This necessity of "finding something" undoubtedly has been responsible for many of the reported abnormalities in epilepsy which crowd the literature Unfortunately, however, errors in the chemical laboratory or at the bedside are not so quickly demonstrable as errors of technique in the bacteriology laboratory

Although no one hopes to find a specific organism that is responsible for seizures, all recognize the importance of infections as a contributing factor Occasionally the eradication of a focus of infection will be followed by cessation of seizures A survey of the bacteriology of the intestinal contents of patients is being conducted by Higgins (personal communication)

#### *Toxicity of blood, urine and spinal fluid*

In any disease of unknown etiology, the idea of a specific toxin is always attractive To this rule epilepsy is no exception

Ceni (1899 to 1906) has been the most prolific writer on this subject He endeavored to prepare an anti-toxin against seizures In his last report (1906) he injected 113 rabbits with increasing amounts (up to 65 cc) of serum from 36 epileptic patients Results were inconclusive Turner (1907) gives references for observations concerning the toxicity of blood, urine and sweat published up to that time Loewe (1911-1913) reported that after a seizure the undialysable portion of the urine produced convulsions when injected into rabbits Pellacani (1914) was unable to demonstrate antibody Meyer (1912) injected 10 to 20 cc of defibrinated blood from patients into the peritoneal cavity of guinea pigs Of 28 experiments in which guinea pigs were injected with blood taken during a seizure, 12 had convulsions and 16 died Of 11 animals injected with blood taken during an interval, 6 had convulsions and 4 died Of 13 animals injected with blood from non-epileptic patients, 1 had a convulsion and 3 died The conclusions are not convincing because of discrepancies in the data presented Preda and Popea (1913) injected serum from epileptics (10 cc per kilo) intraperitoneally into dogs, followed in 24 hours by one-third the amount intravenously Such animals died, whereas others

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injected with serum of normal persons did not. Trevisanello (1913), reasoning that anaphylactic reaction should not result if one of the two injections consisted of spinal fluid, used various combinations of serum and spinal fluid of normal and epileptic subjects. This material was injected into guinea pigs subdurally at intervals of 9 days. In 11 experiments in which serum and spinal fluid were from patients, anaphylactic reaction resulted. In another group in which one or both of the injections was of material from normal persons, no reaction occurred. The material is presented clearly and concisely. Pagniez, Mouzon and Turpin (1921) injected 2 to 4 cc of serum from patients in animals and noted only a myoclonic twitching of muscles. Anthaume and Trepsat (1922) injected 0.5 cc of serum of 6 patients into rabbits. Five of these had convulsions and died. The injection of urine and spinal fluid had no effect. Weichbrodt (1922) injected serum intraperitoneally into mice, but presented no data to support his views. Pfeiffer, Standenath and Weeber (1925) injected 1 cc of serum intraperitoneally in mice. 70 experiments were made with serum from 23 patients. They found no relationship between the toxicity of the serum and the concentration of peptidase. Serum from normals as well as from epileptic patients caused death. Held (1920) injected blood of patients intravenously into rabbits which reacted by twitching of forelimbs and drawing back of the head. Serum and substance of an unnamed gland were taken from these treated rabbits and injected subcutaneously into patients at monthly intervals. Reactions in patients consisted of headache, dizziness and vomiting. He states that approximately 400 patients were treated, in 70 per cent of whom the results were considered favorable. Pagniez (1924) injected 1 cc of serum of patients into the carotid artery of guinea pigs. As a rule spasms resulted. The degree of reaction varied greatly, although he believed that blood taken after a seizure was less toxic. Heating the patient's serum to 58°C. resulted in loss of toxicity.

Cuneo (1913, 1914, 1922, 1925, 1926) believes that he has not only demonstrated a toxic substance in the blood but has identified it as an albumose. His theory, briefly stated, is that because of deficient carbohydrate digestion in the intestines, nucleic and lactic acids are formed, sodium tartrate and acetate are liberated in the blood, which in turn liberate an albumose which causes the seizure. A sympathetic

restatement of his theories has been given by Osnato (1923) Cuneo presents very little real data, and the separation of observations from speculations is not an easy task The various papers yield the following Blood from patients was tested with various reagents In 8 instances blood drawn during or soon after a seizure and especially treated gave a positive Biruet reaction and was precipitated by ammonium sulphate The blood of one patient not having seizure, of three patients with general paresis and of three bulls, did not give these tests (1914) Epileptic patients on carbohydrate diet have acidosis (as measured apparently by litmus paper test of urine, feces and breath) and seizures are increased (No tabulation of data) When fed to patients, sodium acetate and tartrate are not transformed to sodium carbonate as in normal persons When injected into dogs, these substances produce convulsions (1922) (No experimental data) When large amounts of albumose solution are injected intraperitoneally in rats and intravenously into dogs, a severe reaction, accompanied by hypoglycemia, results (1926) Cuneo's experimental data, as published, are too meager to justify drawing any conclusions Some of his statements are so far from the mark (such as the one repeated in his last article (1926) that a carbohydrate diet in epileptics produces acidosis) that one is doubtful of the whole research Catalano (1922) treated 7 patients with sodium nucleinate, suggested by Cuneo, without favorable results

Speransky (1926) froze a circumscribed portion of the cortex of dogs with liquid carbon dioxide, the dura remaining intact From two to thirteen hours later the animals had convulsions without reference to the area treated If the frozen area was removed immediately no convulsions resulted Pieces of necrotic tissue from the frozen area was introduced under the dura of two dogs that later developed convulsions Repeated freezing of the brain in gradually increasing doses allowed 15 per cent of the dogs to survive what would otherwise have been a lethal dose In order to determine if this neurotoxin was in the circulating blood, he transfused 1 cc of the blood of a dog about to die into a normal dog The normal dog became spastic 6 days but no convulsions He was then transfused with blood from immunized animals.

*Summary* Though many authors have found a convulsion-producing toxin in the blood of epileptics, their reports leave us cold. This is because the reactions obtained may have been anaphylactic phenomena, the result of the injection of foreign sera. Most of the experiments were poorly controlled, and the data presented are unconvincing. However, the question is important and some of the experiments, especially those of Trevisanello and of Speransky are suggestive. Certainly the matter deserves more prolonged and careful research.

### *Protein metabolism*

*Constituents of body fluids.* Information concerning incomplete or abnormal metabolism of food substances can be gained only by careful measurements of the constituents in urine, feces, blood or expired air, under controlled conditions of diet and activity. There is a widespread medical opinion that persons with epilepsy have either a derangement of protein metabolism or are peculiarly susceptible to protein food. The basis of this idea apparently lies in earlier investigations of the nitrogenous constituents of urine and feces.

*Urine and feces* It is difficult to summarize the findings of earlier investigators because of the variety of chemical methods used, some of which are now considered obsolete, and because of the discordant results obtained. Here again one is oftentimes at sea because of the apparent failure of some investigators to control food intake or the periods of urine collection, and to obtain control measurements from normal subjects. It seems hardly worth while to attempt analysis of this large amount of material. We shall mention only a few of the observations most often quoted. Rohde (1909) studied three patients. One of these showed a positive nitrogen balance during two periods of study. During a period of 46 days the patient consumed 17 grams of nitrogen more than she excreted. Half of this (8 per cent of the amount ingested) could not be accounted for by an increase in body weight. The protein intake was excessive (2.2 grams per kilo), and it would seem that the importance of the positive balance in this one patient has been overemphasized. Allers and Sacristan (1913) studied four patients for periods of from 4 to 25 days each, recording the uri-

nary nitrogen, urea, uric acid, purin and phosphates They noticed a fluctuation in the nitrogen excretion In some instances there was presumably a negative nitrogen balance, but as fecal nitrogen was not measured regularly, an accurate balance could not be struck Pighini (1913) did a large amount of work on the nitrogenous constituents of the urine and the effect of injection of nucleic acid and other substances Results were negative

We have had unusual opportunity to study the nitrogen excretion of patients during periods of starvation, when the troublesome factors of the nitrogen content of food and feces did not enter in In a dozen such experimental periods we have found marked difference in the amount of nitrogen excreted in the urine with relation to body weight Such individual variations, however, were no greater than have been found in healthy subjects So far as examination of the excretions go, we have no evidence that there is abnormality in the protein metabolism of persons with epilepsy

*Blood* Recent advances in methods of blood analysis have permitted a closer analysis of this question If, as some earlier writers assumed, there is a retention of products of protein metabolism in the body, there should be an increase in the concentration of these substances in the blood

The concentration of urea in the blood was measured in a few patients and essentially normal values found by Obregia and Urechia (1914), Bouttier and Rodriguez (1920), Weston (1920) and Hartenberg (1924) Dufour and Semelaigne (1920) found increase of blood urea before seizure in one case Bruhl (1923) made 60 measurements of blood creatinine in 11 cases of epilepsy He obtained inconstant increase in creatinine, up to 2.16 mgm after seizures On the whole, however, measurements were fairly normal and constant from day to day Frisch and Walter (1922) in 3 patients measured the non-protein nitrogen of the blood 56 times In only 2 out of 8 periods did measurements exceed 40 mgm Wuth (1921, 1925 and 1926, a) has discussed the metabolism in epilepsy and has presented measurements (1922-1926, b and c) of the various non-protein nitrogenous substances in the blood Data concerning 50 patients are presented in detail in his monograph (1922) In general measurements were



within normal limits. Values tended to be higher when blood was collected during convulsions of epilepsy, of general paresis, of hysteria, etc., than during interparoxysmal periods. He attributes these high values to the muscular work involved in the seizures. Lennox, Wright and O'Connor (1924) measured the various non-protein nitrogenous constituents in a large group of patients. Of 163 measurements of non-protein nitrogen made in 123 patients, only 12 were over 40 mgm. Of 137 measurements of blood urea nitrogen, only 1 was above 20 mgm. Of 56 measurements of amido-acid nitrogen, only 1 was above 8 mgm. Of 158 measurements of uric acid, 8 were above the normal limit of 5.5 mgm. Of 77 measurements of blood creatinine, none was above 1.7 mgm. In one case serial measurements were made before, during and after several seizures. These various constituents remained at a constant level. Lennox, O'Connor and Bellinger (1926) have also published measurements of non-protein nitrogen in 10 patients before, during and after periods of fasting. There was some increase in non-protein and urea nitrogen during the first days of fasting, due to increase protein breakdown, but such values were not abnormally high, they did not bear relationship to seizures, and were similar to measurements made in healthy fasting subjects.

The situation with regard to uric acid is of historical interest because of the contention of Haig (1892) and others that seizures are due to a retention of uric acid in the blood. The study by Lennox and O'Connor (1925) of the retention of uric acid which occurs during fasting in both epileptic and normal subjects gives a possible explanation of the abnormal urinary uric acid findings of earlier investigators. During ketosis there is a marked retention of uric acid in blood and tissues with a great out-pouring of the retained product when the acidosis is relieved. As we show elsewhere, there is evident relationship between seizures and acid base changes in the body. The variation in uric acid excretion with relation to seizures may parallel, in a purely passive and incidental way, the variations in the acid-base relationships of the body. The fact that concentration of uric acid in the blood rose as high as 22.5 mgm per 100 cc. of plasma during fasting, when there was reduction in the frequency of seizures, demonstrates that increased concentration of uric acid in the blood plays no part in inducing seizures.

It is evident that the concentration in the blood of the products of protein metabolism which we are able to measure is not abnormal. Any changes which take place with relation to seizures are the result of seizures and not the cause. Observations concerning the plasma proteins, and the anti-proteolytic ferments of the blood are presented elsewhere.

*Spinal fluid* Because, as we have seen, the concentration of the non-protein nitrogenous constituents of the blood in epileptics is normal, we should not expect abnormal concentration of these substances in the spinal fluid. Obregia and Urechia (1919) in 35 cases (74 measurements) obtained such marked fluctuations in concentration of urea in the blood and spinal fluid, before and after convulsions, that one questions the accuracy either of their technique or decimal points. Patterson and Levi (1926) in an unstated number of patients obtained average values for urea of 26 mgm in spinal fluid and 29 mgm in blood. Bouttier and Mestrezat (1920) in one patient found an increased concentration of urea in spinal fluid after status. Laurés and Gascard (1920) in 6 epileptics found the average measurements for urea after convulsions as 55 mgm, in contrast with 28 mgm in 6 patients after hysterical convulsions. Presumably, the increase was due to the muscular work of convulsions. Observations concerning the total protein of the spinal fluid are presented elsewhere.

### *Ferments*

*Anti-proteolytic* The concentration of the various ferments in the blood is a measure of the activity with which the corresponding food materials are being digested. Rosenthal (1910) presents in a clear manner observations of the anti-trypsin titre of the serum of 32 patients, as measured by the amount of casein solution decomposed under standard conditions. Of the 80 examinations made, 46 per cent showed a normal and 54 per cent a high titre. Of the measurements made before seizures, 80 per cent were high and of those made after seizures, only 10 per cent. Three charts are given showing the relationship of anti-tryptic power to seizures. In these there was temporary increase immediately after seizure, due apparently to the muscular work involved. Unfortunately, the observations were too few in number to be conclusive. Pfeiffer and DeCrisis (1913) repo-

increase of anti-tryptic titre at the time of seizures Pfeiffer, Standenath and Weeber (1925, a and b) made more than 500 observations of the peptidase content of blood and urine in more than 25 severe cases of epilepsy. Measurements were made about every other day for as long a period as 36 days. Single urine specimens, of which the volumes were not controlled, were used. Charts, by means of which data are presented, show very marked fluctuations in the concentration of the ferment, both in serum and urine. In the serum it may reach values several times the normal. There is no constant relationship between the concentration in blood and in urine. The high blood values often accompany low values in the urine, suggesting a retention of peptidase in the blood. This apparent retention may precede the occurrence of convulsions or of psychic equivalents, although in the charts not every case of such retention was followed by a seizure. It is difficult to check statements concerning the titre of blood and urine with respect to seizures because the exact time relations of samples to seizures is not indicated. The experiments suggest that there may be an increased permeability of the intestinal wall to the passage of ferments or deficiency in its elimination by the kidneys. Peptidase in itself is not toxic. Therefore, its increased concentration in the serum would be of significance only as an indicator of some factor such as increased decomposition of protein material in the intestines. The use of catharsis reduced the concentration of ferment in the blood. The authors did not obtain a reaction for peptidase in the spinal fluid of two patients.

Frisch and Walter (1922,a) found an increase of anti-tryptic ferment in a patient (5 measurements) as the day of seizure approached, an observation confirmed by Bronfenbrenner (personal communication). Wuth (1922) found what he considers normal anti-trypsin titre (0.821 to 2.302) in 40 patients. Serial examinations were too few to permit statement concerning abnormality with reference to seizures. Sacks and Zander (1927) found slightly subnormal values for catalase and peroxidase in 8 patients.

*Abderhalden reaction* In the days when an Abderhalden reaction was considered evidence of the formation of a ferment to deal with a foreign protein, various authors found positive reactions for brain

substance in patients with seizures Maass (1913) obtained positive reaction in 7 patients Grigorescu (1914) in 60 patients noted positive reactions in an unstated number of cases not only with brain, but also with muscle and gland substance He also injected intravenously 0.5 gram of peptone made from brain substance into a patient with resulting reaction Mayer's (1914) results were negative

These observations concerning ferments are not convincing because the authors do not present sufficient data from control experiments The observations are suggestive enough to justify further study

*Respiratory metabolism* DeCrimis (1925) measured the  $O_2$  and  $CO_2$  in the respired air of 4 patients and 2 normal subjects after the ingestion of meat The patients did not show the expected increase in oxygen consumption and  $CO_2$  elimination The author concluded that in epilepsy there is incomplete combustion of metabolic products We know, however, that healthy individuals differ greatly in their response to the ingestion of food DeCrimis' series is too small to permit conclusions Frisch (1927) had an adequate group of 40 women, 24 of whom showed little rise in oxygen consumption 60 to 90 minutes after the ingestion of meat and rolls Measurements fluctuated so greatly that, in the absence of control data from healthy subjects, one suspects errors in technique

*Effect of protein feeding* Although many clinicians insist on a protein poor diet for their patients, there are almost no controlled observations concerning the comparative effect of high and low protein diets on the frequency of seizures Weeks (1923) and his associates, fed 6 patients for 48 days on an almost pure protein diet (meat, egg white and casein) Although the amount ingested was the maximum that the patients would eat, the diet provided less than half the needed calories The number of convulsions before, during and after this special diet were in the ratio of 100, 80 and 60 respectively Because the group used by Weeks et al received no great benefit even from fat diet, it would seem that they were recalcitrant to therapeutic influences Therefore, there is need for repetition of this experiment with a group of younger, less chronic patients Patients frequently state that if they eat meat a seizure will result One such patient of ours, a young woman of 21, in addition to her epilepsy had essential hypertension For a period of 15 days we gave her only meat to eat,

without thereby inducing either a seizure or an increase in blood pressure. It would seem that a rigid meat free diet is of no benefit to patients and may do harm, through a reduction in body strength or the induction of primary anemia. Because protein food is acid forming, it should on this account prove beneficial.

Though we find no direct evidence of abnormal protein metabolism in persons subject to convulsions, the matter is not closed. Possibly there may be abnormal split products of protein metabolism, which we are at present unable to measure, that play a part. Again it is possible that in epilepsy the body may react in an abnormal manner to normal protein metabolites. Additional information might be obtained from the reaction of the body to the parenteral introduction of protein substances.

*Hypersensitiveness.* Seizures are so swift and dramatic in their appearance that one naturally compares the condition with that occurring in anaphylactic shock. In this condition, there is presumably a disturbance in function of the endothelial cell lining of capillaries, with consequent widespread and profound reaction (Zinsser, 1927). Various writers have pointed out certain resemblances between epileptic seizures and anaphylactic shock, such as leucopenia and lowered temperature.

There is little direct evidence concerning the interrelation of these two conditions. Van Leeuwen and Zeydner (1922) found a toxic substance present in the blood of patients suffering from asthma,

Wallis, Nicol and Craig (1923) performed skin tests upon 122 patients, 37 per cent of whom gave positive reaction to various protein food materials. In a group of healthy subjects 4 per cent reacted. The largest number of patients, 28, were positive for peptone. The authors found that patients who gave a positive reaction were more sensitive before and less sensitive for several hours after a seizure. As a matter of therapy, they endeavored to eliminate the offending protein from the diet. They state that in 13 private cases "good results" followed. Howell (1923) recites 14 case histories in which persons were sensitive to various substances or had seizures after eating certain foods. In two patients arrest of symptoms followed treatment. Cohen and Lichtig (1924) tested 10 patients to 128 proteins. None of the patients showed a reaction which could be correlated with the convulsive seizure. In a group of 250 patients with asthma questioned by them, there was no unusual incidence of epilepsy in the families. Spangler (1927) obtained a family history of allergy in 88 out of 100 epileptic patients. He had no control data. Ward and Patterson (1927) carried out skin tests upon a group of 1000 patients with a large number of substances. Forty-seven per cent of these patients gave a positive reaction, in contrast to 8 reactors in 100 non-epileptic subjects. Unfortunately, the authors do not state their criterion of a positive reaction. More than one-half of the reactions counted as positive were tabulated as "plus or minus." Eastlake's (1925) patient reacted to many animal proteins, and had an almost fatal convulsion when given an injection of 4 drops of sterile beef broth. One of our patients gave a positive reaction for feathers, and was better when removed from contact with them. Our triumph was short lived, for seizures recurred and autopsy revealed a glioma of the brain. Another patient with frequent seizures reacted to streptococci and following the removal of an infected tooth had no seizures for seven years—when they recurred.

The fact that among patients with epilepsy the incidence of allergic conditions, such as hay fever, asthma, sensitiveness to horse serum, etc., is not great, is against the importance of this factor in any but the exceptional patient. We have spoken already of features which some writers interpret as anaphylactic phenomena, e.g., the

hemoclastic crisis of Widal, Abderhalden's reaction, and the reaction in animals following the injection of blood from epileptic patients. Additional circumstantial evidence concerning the results of protein injections in epileptics follows.

*Protein injections.* Miller (1924) has treated patients with migraine successfully by intravenous injections of peptone. He calls attention to the fact that epilepsy and migraine have much in common and that similar benefit might follow the use of peptone injections in epilepsy. McCready and Ray (1924) and Roddis (1925) present arguments, but no new data. Auld (1920) and Edgeworth (1920) have used peptone treatment. The latter gave intravenous peptone injections in 23 patients, in 9 of whom there was suppression of spells "for months."

A more potent and dangerous material for injection is rattlesnake venom (crotalin), the empiricism of which is founded on the circumstance that a patient in Texas was free from seizures after being bitten by a rattlesnake. Spangler (1918 and 1925) stated that he has treated 400 patients with more than 10,000 intramuscular injections. He believes that the eosinophilia which follows injections is a measure of the clinical improvement. In 25 patients showing eosinophilia, attacks in one-half have been absent for a period of from 2 to 5 years. In addition, he has advocated (1924) the use of glandular substances. Spangler's work deserves little attention because of his failure to present the therapeutic results obtained in his large group of treated patients. Fackenheim (1926) states that of 50 patients treated since 1910, 20 have been free of attacks. Crotalin injections have proved useless or worse in the hands of Jenkin and Pendleton (1914), Thom (1915), Russell (1922) and Reinthal (1924).

A rather more innocuous form of protein therapy is that of intramuscular injections of milk. Dollken (1920) and Janota (1923) saw and Weidner (1924), Schwartz (1925) and Becker (1924) did not see benefit from its use.

Injection of Pasteur anti-rabic vaccine is yet another form of parenteral protein injection. Ossokin and Ochsenhandler (1924) treated 28 cases, a fourth of whom were "much improved." Horoshko (1925) treated 20 cases, as many as 100 daily injections being given. Improvement resulted in many cases. Milizyn (1926) gave 90 daily

injections in 69 patients, in 38 per cent of whom improvement in frequency of seizures and in mental condition resulted

Empiricism knows no bounds in the treatment of epilepsy. Several authors have given patients injections either of the patient's own or of normal human blood. Suttel and Arsac (1924) give an amusing account of a horse with a diseased hoof which they treated by repeated subcutaneous injection of 2 cc of serum from an epileptic patient. Eventually the horse recovered, the result being attributed to the healing properties of the epileptic blood.

*Summary* The only direct evidence of abnormal protein metabolism in epileptics is the increased blood fibrinogen and spinal fluid protein and the increased anti-proteolytic ferments which a minority of patients show. Allergic phenomena are present in the occasional patient. There is no convincing evidence that the eating of meat or other protein food influences attacks.

#### *Carbohydrate metabolism*

The question of the concentration of sugar in the blood of persons subject to convulsions has received little attention. This is perhaps due to the fact that interest has been focused on the protein metabolism.

*Insulin convulsions* The discovery that insulin hypoglycemia in rabbits is accompanied by convulsions has thrown the question of carbohydrate metabolism in epilepsy into the foreground. Although convulsions, as a feature of hypoglycemic reactions, are much less frequent in man than in animals, they do occur. The mechanism by which such convulsions are produced is yet a matter of debate. MacLeod (1926) has recently discussed the explanations which have been advanced, viz, a disturbance of the balance of glucose within and without the nerve cells, anoxemia of nerve cells and an interference with afferent impulses from the labyrinths. Interesting observations concerning the glycogen content of the brain in animals with convulsions have been presented in the section dealing with functional instability of the brain.

Increased irritability of muscle or nerve to galvanic stimuli, associated with insulin hypoglycemia has been found in non-epileptic



patients by Behrendt and Hopmann (1924) and Waltner (1925) and in animals by Greisheimer (1925) These observations make it pertinent to inquire whether persons subject to periodic convulsions show diminished concentration of glucose in the blood, either constantly or with relation to seizures

*Sugar in blood and urine* Certainly there is no marked coincidence of diabetes and epilepsy The following authors have measured blood sugar in the stated number of epileptic patients, viz , Weston (1916) six, Heidema (1919) five, Kooy (1919) eight, Kersten (1921) eighteen, Schwab (1922) ten, Wuth (1922) forty, Barlocco (1922) five, Olmstead and Gay (1922) twelve, Weeks, Renner, Allen and Wishart (1923) forty-three, Shaw and Moriarty (1924) five, Holmstrom (1924) twenty, Nielson (1925) fifty-four The authors with the large groups of patients found normal values Lennox, O'Connor and Bellinger (1927) made 512 measurements in 270 patients The normal values obtained in this large series demonstrate that during the interparoxysmal period, the concentration of sugar in the blood is normal. In fasting, as Shaw and Moriarty (1924) and Lennox, O'Connor and Bellinger (1926) have shown, blood sugar in these patients is at a constant low level and seizures are reduced in frequency

The question next arises as to whether significant changes in the concentration of blood sugar occur with reference to convulsions. Kersten (1921) presents 18 curves showing the concentration of blood sugar at frequent intervals throughout the day. Fourteen of these curves were made on days in which patients had seizures He states that low values were found in the half hour or hour preceding seizures, and higher values during the several hours following Inspection of the curves, however, shows that this was not always the case The fluctuations in the sugar level were so violent—between 40 and 220 mgm , that one suspects errors in analysis, or that the influence of food was not taken into account Kersten sees in the fluctuating levels of blood sugar an evidence of fluctuations in the activity of the adrenal glands In contrast with these observations, Holmstrom (1924) in several patients found very slight changes in blood sugar level, i e , from 80 to 104 mgm , a variation no greater than occurs in

normal individuals The author states that seizures occurred at the low points in the curves He attributed the observed fluctuations to disturbance of the sympathetic system Vollmer (1923) saw in the decrease in concentration of sugar which occurred before a seizure in one of his patients, evidence of altered acid-base relationships The observations by Frisch and Walter (1922), by Wuth (1922), Barlocco (1922) and Pezzali (1923) are too fragmentary to permit conclusions Cuneo (1925) observed hypoglycemia after convulsions in a small group of patients Metcalf and Moriarty (1926) reported a great increase in sugar, up to 312 mgm in blood collected during convulsions from a patient with nephritis

From frequently repeated measurements made in a patient having serial convulsions, and in a healthy person who simulated convulsions, Lennox, O'Connor and Bellinger (1927) concluded that any increase in blood sugar which takes place during convulsions is the result of the muscular exertion and asphyxia of the seizure, and whether blood sugar increases depends on the amount of readily available glycogen in the body They believe that in the usual case of epilepsy there is no evidence that blood sugar plays any more than a passive rôle in the events associated with seizures In the unusual patient, extreme hypoglycemia may assist in the precipitation of seizures One of their patients was a severe diabetic whose first convulsion had followed an overdose of insulin On seven occasions the patient was given a large dose of insulin with depression of blood sugar to below 50 mgm, accompanied by hypoglycemic reaction On two occasions, when blood sugar was at its lowest point, the patient had a generalized convulsion, and on another occasion, when blood sugar was only 25 mgm, he was mentally confused but had no convulsion On other occasions, in contrast with the cases reported by Miller and Trescher (1927) and by Harrop (1927), he had convulsions not related to insulin injections when the concentration of blood sugar was normal

*Spinal fluid* Only scattered observations of the sugar content of the spinal fluid have been reported Thabuis and Barbé (1913) in 7 patients found values between 20 and 43 mgm Wittengenstein (1923) in 10 patients found values from 45 to 89 mgm In three instances sugar was higher a few hours after seizure than before

ments, a decreased concentration before the fit Osnato and Killian (1927) obtained variable values not only in patients but also in healthy subjects

Pighini (1910) in 25 epileptics, found crystals of cholesterin in the spinal fluid of 10 Goebel (1924) in an unstated number of patients found increased amounts of cholesterol in the spinal fluid before seizure. Osnato and Killian (1927) obtained a measurable amount in only one of 22 patients examined

*Respiratory metabolism* DeCrisis (1925) in one patient obtained somewhat abnormal values for oxygen consumption and the respiratory quotient following the ingestion of fat Geyelin (personal communication) in observations made on patients on high fat diets obtained extremely low respiratory quotients, which he could explain only on the grounds of an abnormal metabolism of fat This subject is receiving attention at the Russel Sage Institute

*Effect of fat feeding* Epileptic patients have an unusual ability to consume and metabolize fat, and while on a fat diet many of them show a striking reduction in the frequency of seizures Because this effect is apparently associated with changes in acid-base equilibrium, the observations are discussed in the following section.

As to other constituents of the diet, the effect of the ingestion of certain of the mineral salts will be discussed in the next section As to vitamins, only Tracy (1926) has attributed seizures to their absence from the diet.

*Summary.* Although there is no conclusive evidence of a disordered metabolism of fat in epilepsy reported abnormalities require further investigation Amelioration of symptoms may accompany incomplete oxidation of fat, due to the resulting decrease in irritability of nerves

### *Acid-base equilibrium*

*Urine.* The principal recent work on this subject comes from Copenhagen where a group of workers have observed a constant abnormality in the proportionate amount of ammonia eliminated by epileptic patients Observations have been presented as follows.

Bisgaard, Jarlov and Nørvig (1918), Jarlov (1919), Bisgaard and Nørvig (1920), Larsen (1921), Nørvig (1921, a and b), Bisgaard

(1922), Bisgaard and Nørvig (1923), Schrøder (1923), Nørvig and Larsen (1924, a and b), Nørvig (1924), Bisgaard (1925), Schou and Teglbjoerg (1925) and Teglbjoerg and Madson (1926)

As these various authors apparently used the same methods and material, we may summarize their findings as follows. Hasselbalch in 1916 showed that in healthy subjects the ratio of ammonia nitrogen to the total nitrogen of the urine, if plotted against the pH of the urine, gives a value which is fairly constant. In conditions in which there is ketosis, this quotient is greatly increased, and the condition is spoken of as "dysregulation". According to Nørvig (1924) 21 epileptic patients and 10 normal subjects have been investigated. Some 1000 measurements of the  $\text{NH}_3\text{N}/\text{T N}$ —pH ratio have been made. In all cases of essential epilepsy examined, except two in which focal brain lesions were found, the above mentioned quotient varied widely from day to day. Because pH of the urine remained fairly constant, the fluctuation in the reduced ammonia value was due to excessive output of  $\text{NH}_3$ . This output was not related to seizures except that fluctuations were greater when seizures were more frequent. The authors found a similar condition in tetany and parathyroidectomized animals. Feeding of gland substance to such patients and animals partially overcame the dysregulation. For these reasons the authors believe that seizures are a symptom of endocrine disturbance, the treatment of which should be administration of parathyroid gland and sulphuric acid. They conclude that in epilepsy, ammonia is produced in the body without respect to body needs, and the body lacks the normal ability to dispose of the excess of acid or of alkali. Subsequent investigation has shown the writers that this "dysregulation" occurred in an occasional patient without epilepsy, e.g., patients with encephalitis, dipsomania, dyspepsia, and the healthy mother of an epileptic. Moreover, Jensen (1925) reported three and Reiter (1925) two epileptic patients who showed no dysregulation. Rafflin (1925) also disagreed, though he presented but fragmentary data.

The demonstration by Benedict and Nash (1926) that ammonia is formed in the kidney and serves to maintain a normal pH in the urine, takes the main support from Bisgaard's conception of  $\text{NH}_3$  as

important regulator of neutrality in the body Erickson, Levinsen and Warburg (1927) have critically examined the ground covered by Bisgaard "Dysregulation," they conclude, is neither specific for epileptics nor constantly found in them It may be caused by deficient food intake or by insufficient function of the respiratory center

Gamble and Hamilton (1927) performed a carefully controlled experiment of 27 days, during which the child being studied had four two-day periods of seizures The diet was accurately constant as regards its acid-base composition A large increase in total acid excretion, mostly due to chloride, paralleled by increase in total fixed base, mostly sodium, occurred during periods of seizures. The authors are not sure how much of this increase in acid excretion was the result of the increased activity from seizures. During the latter part of the experiment, seizures were controlled by large doses of luminal There was increased acid and base excretion on the days when seizures were due, though this was not as great as occurred with seizures. During the period of observation, the pH of the urine and its ammonia content were not appreciably altered

The observations of Stuurman (1923-1924) are almost without value because of the inadequate methods used Vollmer (1923 and 1925, a and b) made frequent measurements during the day of titratable acidity, pH and phosphate of the urine of children He noted that the acidity was decreased before seizures and increased after.

*Blood and spinal fluid* Studies of the relationship of acid-base changes in the body to convulsive seizures offers a most promising field of investigation Twenty or thirty years ago when the medical world believed that "acidosis" was the cause of various morbid conditions, it was often stated that persons with epilepsy presented evidence of a decreased alkalinity of body fluids Because of the lack of exact methods for measuring acid-base relationships, such statements were, of course, without foundation

The observations of Charon and Briche (1897), Pugh (1902), Schultz (1907), Frisch and Walter (1922) and DeCrisis (1925), most of whom reported the blood as less alkaline than normal are now without value. Nevertheless their conclusions are even yet being quoted The animal experiments of Elias (1918) cannot be dismissed so quickly.

He injected various acids intravenously into dogs. Following such injection there was increase in nervous irritability and in some instances convulsions, which could be arrested by intravenous injection of bicarbonate. The degree of acidosis obtained was not measured. Opposite conclusions were reached by Frohlich and Solé (1924) and Lennox and Beetham (1928).

*Hydrogen-ion concentration* The hydrogen-ion concentration of a fluid is the ratio between its acid and basic elements. pH may be measured by electrometric or colorimetric methods. In normal persons, according to Cullen and Austin (1925), pH of the blood plasma may vary between 7.30 and 7.50, a wider range than was at first recognized.

Jarlov (1921) without presenting data, stated that he has found blood as alkaline as pH 7.42 in epilepsy. Geyelin (1923) was the first to work extensively on this subject. He stated that daily measurements of the pH of the blood plasma of patients showed no curve definitely characteristic of epilepsy, but there was a distinctly wider range of blood pH from day to day and from hour to hour in epileptics than in normal persons. Bigwood (1923 and 1924, a and b) has published data concerning ten patients studied while working with Geyelin and 30 patients studied subsequently in European clinics. Data (1924b) are presented by means of a series of charts. The pH of the plasma was measured by the colorimetric method of Cullen. In all, 380 measurements were made. Periods of observation varied from one week to three months, during which time blood was taken every other day. Various experimental procedures, such as the use of fasting, bromide, luminal and calcium chloride were tried. The following is a summary of Bigwood's observations, so far as they concern plasma pH. Taking normal values for pH as 7.33 to 7.39, 25 epileptic patients on at least one occasion, showed an abnormal reading, the extreme limits being 7.26 and 7.48. In general, alkalosis preceded seizures. There was no relationship between the degree of alkalosis and the severity of seizures. During a long period without seizures the pH might remain normal. In some instances an increased alkalinity of the blood was not followed by a seizure, also a seizure might occur without preceding increased alkalinity. Cases

with psychic manifestations, petit mal, etc., without convulsions, did not show such marked fluctuations in pH. Plasma pH was normal in 5 out of 6 patients with Jacksonian epilepsy, and in one case each of hysteria and syphilis with convulsions. Various measures, such as fasting and high fat diets and the administration of HCl and borotartrate caused a decrease in the alkalinity of the blood and a decrease in seizures. Bigwood further believes that the tendency towards alkalosis is not due to over-ventilation, as shown by normal measurements of blood and alveolar  $\text{CO}_2$ . In subsequent publications he explains convulsions on the basis of diminished concentration of ionized calcium in the blood. These observations will be presented later.

Frisch and Fried (1926) considered Bigwood's measurements erroneous because the factor for protein used in Cullen's method is not applicable to serum from epileptics, who have a defect in their protein metabolism. They measured the pH of the serum of 23 epileptic patients, using the colorimetric method of Hallo and Weiss. This method, they say, gives a value for normal serum of from 7.48 to 7.58. They concluded that there is no displacement of the pH in epilepsy, although inspection of their measurements, of which 105 in all were made, shows considerable fluctuation in values, between 7.45 and 7.77. Of the 9 patients whose blood was examined on 7 or more occasions, all but one, on one or more occasions, had a value outside the limits of the authors' normal range. Seven of the nine showed a measurement more alkaline than 7.58. The time relationships of venesection to seizures is not clearly indicated. Marrack and Thacker (1926a) using the colorimetric method, in 8 patients examined found pH values within normal limits. Dautrebande (1926) measured the pH of the blood in 7 patients. Using the Cullen method, values between 7.37 and 7.52 were obtained, the average of 26 measurements being 7.46. The Hasselback method, in which pH is calculated from measurements of the alveolar  $\text{CO}_2$  and the  $\text{CO}_2$  tension of the blood, in 14 measurements gave an average of 7.36. Such discrepancy was not found in non-epileptic patients. The author explains the relatively high values obtained by the Cullen colorimetric method by supposing that there is an alkaline substance

in the blood of epileptics which does not combine with  $\text{CO}_2$  in vivo. Proof of such a conception would require the presentation of more data than the author gives.

Measurements of the pH of spinal fluid have been reported by Patterson and Levi (1926). The average value for the group was 7.75. The abnormality was so great, amounting in some instances to an extreme alkalinity, that one must suppose the authors were not able to check their standard solutions against electrometric measurements. Georgi (1926) states that he has often observed preaproxymal alkalosis but does not give the method used nor present data. Osnato and Killian (1927) obtained normal pH values for spinal fluid.

TABLE 2  
*Acid base composition of normal blood plasma*

BASE	N/10 SOLUTION PER 100 CC PLASMA	PER CENT	ACID	N/10 SOLU TION PER 100 CC PLASMA	PER CENT
Na'	143.4	91.9	$\text{HCO}_3'$	27.0	17.3
K'	5.1	3.3	Cl'	103.0	66.0
Ca"	5.0	3.2	$\text{HPO}_4''$	3.0	1.9
Mg"	2.5	1.6	$\text{SO}_4''$	1.0	.6
$\text{NH}_3$	Insignificant	Tr	Organic acid	2.0	1.2
			Protein	20.0	12.8
Total	156.0	100.0		156.0	99.8

If we accept 7.30 and 7.50 as the limits of normal values for pH of the blood, none of the dependable previously mentioned observations demonstrated an abnormal equilibrium. They do seem to show, however, that in epileptics there is, within this normal limit, an unusual degree of fluctuation from day to day with a tendency to approach a more alkaline reaction.

It is possible for the pH of fluid to be normal and yet for both acid and base elements, simultaneously to be either abnormally increased or decreased. We need to know, therefore, the concentration of the various constituents which go to make up the acid-base ratio. Gamble, Ross and Tisdall (1923) list these substances and express their relative values in terms of cc of 0.1 normal solution per 100 cc of plasma (table 2).



*Base substances.* Because the amount and relative proportion of the four basic elements is of such importance in maintaining the function of body cells, it is important to know if their concentration in body fluids of patients with epilepsy is normal. Comprehensive observations are few. The most important are by Hamilton (1925). He made very careful measurements of chloride, bicarbonate, inorganic phosphorus, total fixed base, and calcium in the serum and spinal fluid of 17 patients with epilepsy. He found these substances present in essentially normal amounts. Furthermore the ratio of their concentration in serum and in spinal fluid followed Donnan's theory of membrane equilibrium. Gamble and Hamilton (1927) in a single patient found no significant alterations in the concentration of fixed base, chloride, bicarbonate, or the pH of blood plasma with relation to seizures. Blumgarten and Rohdenburg (1927) found normal values for sodium, potassium, magnesium and calcium in the whole blood of four patients with epilepsy.

*Plasma bicarbonate.* Sodium represents 92 per cent of the basic elements in blood serum. In the absence of conditions, such as disturbed respiration, which might upset the normal acid-base ratio, measurement of Na (through determining the amount of  $\text{CO}_2$  which will combine with the blood or plasma) offers a ready clinical method for determining the presence of acidosis or of alkalosis. Mørdre (1922) measured the plasma bicarbonate 21 times in 5 patients. The average reading was 65 volumes per cent. He produced an insignificant increase in one patient without inducing a seizure. Frisch and Fried (1926) made 56 measurements of blood bicarbonate in 12 patients, using the method of Hallo and Weiss. Values between 43.5 and 78.4 volumes per cent were obtained. They considered these normal. Dautrebande (1926) made 22 measurements of 7 patients. Values varied between 55 and 65.7 volumes per cent. He considered daily fluctuations abnormally large and believed the blood of epileptic patients tended to be abnormally alkaline, but observed no relationship between alkalinity and the occurrence of seizures. Lennox and Allen (1928) have measured the plasma bicarbonate of 100 patients. All but 12 of these measurements were within the normal limits of 55 and 70 volumes per cent. Abnormality when present was in the direction of increased alkalinity.

*Calcium.* Though calcium constitutes only 3 per cent of the total

base in blood serum, its possible variation in epilepsy has interested many workers. This is because of the well known relationship between increased irritability of nerves and decreased concentration of blood calcium in tetany and the relation of calcium to the permeability of capillaries. This question is discussed at length in the sections on parathyroid glands and on hyperpnea. Here we shall discuss only the concentration of calcium in body fluids.

Measurements of blood calcium made by Frisch and Weinberger (1922) in 3 patients and by Pezzali (1923) in 5 are so diverse that one doubts their accuracy. Vollmer (1923) without presenting data, states that measurements of blood phosphate and calcium are not changed in epilepsy. Reiter (1925, in 12 patients obtained values between 8.3 and 11.5 mgm. He considered these low. There was no change with relation to seizures. There was considerable variation in the measurements made on 3 different occasions in each patient. Sachs (1926) found normal or high values in 8 patients examined twice a week. In several instances measurements were higher at the time of seizure. Talbot and Moriarty (personal communication) found normal values in children both for phosphate and calcium.

The measurements which have been given are for total calcium. Bigwood (1923, and 1924a) believes that in patients with epilepsy the significant thing is the reduction in the blood of ionized rather than of total calcium. Ionized calcium was computed by a formula using measurements of the pH and the  $\text{CO}_2$  tension of the blood. Curves in the charts, therefore, represent the same experimental periods and follow in general the previously reported curves for blood pH. They indicate that in general low concentrations of the ionized calcium preceded seizures. The variations in actual measurements, however, were small.

If, as Marrack and Thacker (1926b) believe, the calcium of the spinal fluid is in the ionized form, its measurement should permit an evaluation of the views expressed by Bigwood. The authors found normal values in the spinal fluid of a small group of epileptic patients. The normal measurements made by Hamilton (1925) have been mentioned. Lennox and Allen (unpublished data) have measured calcium in 100 patients. High and low values in the serum or plasma

were 11.5 and 7.8 mgm, and in the spinal fluid 5.5 and 4.5 mgm. The ratio of spinal fluid to blood calcium was between 41 and 55 per cent, a normal ratio. Except for one case of tetany and convulsions reported by Liu (1928), we have seen no observations concerning the calcium balance in epilepsy.

Tracy (1926) exhibits an x-ray of a patient that shows a decrease in density of the bones, due, he suggests, to loss of calcium salts. This observation would need extension before it could be given weight.

The various observations demonstrate normal values for the calcium in blood and spinal fluid. Clearly epilepsy is not tetany. The two conditions, nevertheless, as we saw when we considered the parathyroid glands, have much in common.

*Ammonia.* Ammonia is present in the blood in such insignificant amounts that it plays practically no part in acid-base relations. Bisgaard and Nørvig (1923), however, considered it significant that they found as much as 1.42 mgm of ammonia per 100 cc of blood. Bigwood (1924) said he found normal values in epileptics, but did not give data. Luck, Thacker and Marrack (1925) in 10 epileptic patients found concentrations between 0.06 and 0.32 mgm. In non-epileptic patients, measurements were from 0.02 to 0.37 mgm. They remind us that during starvation the concentration of ammonia in the blood is increased and seizures are decreased.

*Acids.*  $\text{HCO}_3'$ , chloride and protein constitute all but about 4 per cent of the acid substances of the plasma. Of these  $\text{HCO}_3'$  closely parallels pH and is therefore presumably normal in epilepsy. The concentration of plasma proteins, which we have discussed in the section dealing with blood, is also essentially normal.

*Phosphates.* Concentration of inorganic phosphorus, which constitute about 2 per cent of the total acid of serum, has been found normal by Hamilton (1925), by Talbot and Moriarty (personal communication) and by Osnato et al (1927).

*Chloride.* Chloride constitutes about 66 per cent of the total acid of plasma. It has been accused of increasing irritability of nerve cells, the elimination of NaCl from the diet is an accepted procedure with some physicians, therefore an inquiry concerning the concentra-

tion of chloride in body fluids is of particular interest. Normal values for NaCl may be placed between 450 and 500 mgm for whole blood, and 570 and 620 mgm for plasma.

Weston (1920) in 10 patients obtained values between 480 and 512 mgm for whole blood. Frisch and Weinberger (1922) in 3 patients measured sodium chloride 38 times. They state that low values preceded the occurrence of seizures, in one patient reaching the unbelievably low figure of 210 mgm. They assume that the low concentration in the blood indicates retention of chloride in the tissues, which with accompanying edema of the brain might cause convulsions. The theory is reasonable, but the laboratory data are both fragmentary and unreasonable. Pezzali (1923) in 5 patients obtained somewhat higher values during or after seizure than before. Weeks, Renner, Allen and Wishart (1923) in 43 patients examined found that values in the plasma lay between 536 and 626 mgm. The rather low values encountered were attributed to the salt poor diet which patients had been receiving. Sherrill (1924) in 5 patients found an average value for plasma of 580 mgm. Hamilton (1925) in 17 patients and Lennox and Allen (unpublished data) in 100 patients, found a normal concentration of NaCl in the blood plasma and the spinal fluid and a normal ratio between the NaCl content of the two fluids. This last observation is of importance because it suggests that a normal relationship exists between the concentration of NaCl in blood and tissues.

Concerning the effect on seizures of altering the salt content of the blood, Weeks et al (1923), Sherrill (1924) and Lennox and Allen (unpublished data) found that the NaCl of the blood of patients was reduced by fasting or a salt poor diet. The last named authors obtained a coincident reduction in seizures during fast, but found that administration of salt for short periods during fast with a marked retention of salt in the body was not accompanied by a return of seizures (see fig 12). In one patient intravenous injection of hypertonic saline solution apparently decreased somewhat the length of time required to produce seizure by over-ventilation. Increasing the concentration of plasma chloride by administration of large amounts of  $\text{CaCl}_2$  resulted at first in a reduction in seizures, followed later by

a great increase (fig 10). Freudenberg (1926) in a single patient found that a salt poor diet and 10 grams of bicarbonate a day resulted in a low concentration of chloride in the blood. This condition was accompanied by an amelioration of symptoms. Over-ventilation produced a tetany-like seizure when NaCl was given and a seizure without tetany when NaCl intake was reduced. The author concluded that the reduction of chloride ions rather than the alkalosis was the factor of importance in reducing seizures.

Vollmer and Serebrijski (1926) in observations of a boy who was given fasting treatment and various diets, found that the concentration of chloride in the blood varied between 396 and 559 mgm, except when the patient was given salt, at which time it reached as high as 645 mgm. The authors believed that increase of chloride in the blood was the factor of importance in increasing seizures. However, seizures occurred so infrequently and experimental procedures were varied so frequently that the relationship between seizures and the salt content of the blood was by no means certain.

In any such studies it is necessary to measure not only the concentration of chloride in the blood, but the chloride balance as well. In spite of the unconvincing nature of the evidence concerning the relation of the level of chloride in the blood to seizures, these observations and the fact that tetany in animals can be produced by intravenous injection of NaCl make it seem not improbable that increased concentration of chloride in nervous tissues may play a contributory part in seizures.

*Organic acids.* As to the presence of organic acids in the body fluids, Glaser (1926) obtained normal values for lactic acid in the spinal fluid of three patients. Osnato and Killian (1926-1927) in 35 of 40 patients examined, found lactic acid of both blood and spinal fluid increased, on the average, 74 per cent above normal. We wonder if anoxemia, which causes increase of blood lactic acid, was responsible. Prior and Edwards (1926) obtained a reaction for acetone in the spinal fluid of 10 out of 53 patients in status. Presumably this was due to starvation ketosis.

*Summary.* We believe that in patients with epilepsy in the inter-paroxysmal periods, the acid-base balance in the body fluids is essentially normal. Within the normal limits, there may, however, be

an abnormal degree of variation from day to day. During and immediately after seizures, as a result of asphyxia and muscular contraction, there is a temporary condition of acidosis.

### *Effect of induced alkalosis*

The effect of altering the existing acid-base balance in certain patients with epilepsy is striking.

*Administration of alkali.* The measurements of the reaction of the blood by Charon and Briche (1897) have been quoted as supporting the theory that acidosis is present in epilepsy. They reported, however, that eight patients who received subcutaneous injections of alkaline solutions showed increased frequency of seizures. In the instances quoted by Labbé (1920) in which patients with diabetic acidosis had convulsions, a perusal of the case reports shows that many of these patients were receiving heroic treatment with bicarbonate. We have noted in a previous section that tetany may be precipitated by the administration of alkali. In addition to these observations on patients, Claude, Raffin and Montassut (1926) performed experiments with dogs, measuring the pH of the blood by the colorimetric method of Hastings. They found that normal values lay between 7.33 and 7.40. They then applied a solution of zinc to the cortex and injected sufficient bicarbonate to change the pH to 7.50. This degree of alkalosis was not followed by convulsions. They concluded, therefore, that in dogs with cortical lesions, the production of alkalosis in itself was not sufficient to cause convulsions.

Certain observations made by us are represented in charts which follow. In patient L. R. (fig. 14) alkali was given for two days during a period of fasting. There was some increase in the daily number of petit mal. In this instance, although plasma bicarbonate was greatly increased, the degree of ketosis was presumably increased also. In patient H. G. (fig. 11) alkali was given on two occasions at the end of periods of induced acidosis, one from administration of  $\text{CaCl}_2$  and the other from fasting. In both instances the sudden swing from acidosis to alkalosis was accompanied by a great increase in the frequency of seizures. In another patient (fig. 10) the feeding of large amounts of alkali produced little alkalosis and no increase in seizures.

As a result of these and other observations, we believe that whereas a continued artificial alkalosis may not be associated with an increase in seizures, any sudden upsetting of the acid-base balance toward the alkaline side may have such effect

*Hyperpnea* A new method of studying convulsions has been opened through the observation that seizures may be induced by over-ventilation of the lungs

Rosett (1924) made important observations on various nervous conditions, including a patient with Jacksonian epilepsy, by this method Foerster (1924, 1925a) tested the effect in 45 epileptic patients With the patients sitting he had them forcibly expire for a period of 10 minutes In 25 patients a seizure resulted On repetition of the test, in the majority of cases seizures resulted only occasionally. The induced spells in the same individual were similar Some patients responded with narrowing of the field of consciousness, some had amnesia for the attack. In 43 patients after 6 minutes of over-ventilation there was increased irritability of muscles, as shown by cathodal opening contractions with less than 5 milliamperes of current. In patients who did not have seizures, increased irritability occurred just the same Dalma (1925) in 15 cases produced seizures in 3 Stertz (1925) produced seizure in one out of 8 cases. He found no difference in the reaction between epileptic and psychopathic patients. Guillin, Alajouanine and Thevenard (1925) produced seizure in a patient with Jacksonian epilepsy. He had the same aura as preceded his spontaneous seizures. Janota (1925) in 51 patients produced a seizure in only two (though breathing was forced for as long as an hour). Because these patients were subject to frequent spontaneous seizures, he considered his results negative Hysterical symptoms resulted in two patients He found no change in electric excitability. Mainzer (1925) in 14 patients with epilepsy or hysteria was able to induce seizure in only two He believes that an irritation of the central nervous system from changes in osmotic pressure or from a specific action of the chlorine ion are responsible, for during over-ventilation the concentration of blood chloride increased 4 per cent In a more recent article (1926) he gives in greater detail experiments with a patient with traumatic epilepsy.

This patient constantly had a convulsion after over-ventilation. Intravenous injection of soda bicarbonate or calcium chloride was without effect. In three instances intravenous injection of an unnamed amount of 10 per cent sodium chloride produced seizures. Because such injection was accompanied by an increased bicarbonate content of the blood plasma, it is not clear whether the convulsion was related to the increased blood chloride or to the alkalosis. Grinberg (1925) reported experiments on two epileptic and two hysterical patients. Three of these reacted to over-ventilation with typical seizures. Meyer (1925) secured seizures in 3 out of 20 patients. Frisch and Fried (1926) tried the test in a number of patients, but obtained a seizure in only one. Heidrich (1926) in 20 patients with traumatic epilepsy, elicited symptoms in 7 which pointed to the site of the lesion, as afterwards found at operation. In two of these, Jacksonian seizures occurred, which were duplicated by faradization of the cortex at operation, but which could not be induced by over-ventilation after the operation. In other patients the administration of various glands of internal secretion did not effect results. Lange and Guttmann (1926) observed a patient in whom seizures followed both voluntary over-ventilation and a hysterical attack associated with hyperpnea. Liebers (1926) performed overventilation with 30 epileptics whose electrical reactions he tested before and at intervals after the test. Although only rarely did patients show over-excitability of motor nerve, before the test, 50 per cent showed increased excitability after 10 minutes of over-ventilation. In two cases, seizures resulted and in several others there were various symptoms such as dizziness and spasm of isolated muscle groups. He sometimes obtained Parkinsonian tremor or erythema of the neck and chest. Smirnov (1926) in 41 war wounded soldiers obtained seizures in 9 and abnormal signs, such as positive Babinski reflex in 15. Of 28 non-military patients, 10 had seizure. Georgi, et al (1926) saw spells in 26 of 66 epileptics tested. Sterling (1926) tested 200 epileptics and 100 normals. One-third of the former and none of the latter had a reaction. Schuster (1926) in observations with 7 patients obtained either convulsion, mental confusion, or loss of consciousness. Muck (1926) experimented with 17 women who were subject to migraine. Following over-ventilation, 12 of these patients complained



of pressure in the head which bordered on a headache Twelve normal men had no headache Hendriksen (1927) in 67 patients with epilepsy obtained a seizure in 7 and a loss of consciousness in 7

These various authors witness the fact that in a small proportion (up to 50 per cent) of the patients tested, voluntary hyperpnea was followed by a seizure or its equivalent They do not indicate whether the successful results occurred in patients having the more frequent seizures We have very easily induced fits in patients having frequent daily seizures (figs 7 and 8)

The important question next arises, what is the mechanism by which over-ventilation produces convulsive phenomena in persons subject to seizures? Concerning the effect in healthy persons, Collip and Bachus (1920) and Grant and Goldman (1920) demonstrated that over-ventilation may cause tetany or even, in one experiment by Grant, a tonic convulsion The last named authors showed that this phenomenon was related to the increased alkalinity of the blood, consequent to the "blowing off" of  $\text{CO}_2$  The decrease in total calcium of the blood was slight Freudenberg and Gyorgy (1923) believed that decrease in ionized calcium (which depresses respiration) and increase in phosphate (which stimulates it) were the important factors Duzár and Hensch (1926) observed in children that either a period of over-ventilation insufficient to cause tetany, or the administration of bicarbonate, if followed by the injection of adrenalin will produce tetany. This introduces a new factor for consideration A reverse relationship between over-ventilation and tetany is indicated by the statement of Collip (1926) that in about one-half of his parathyroidectomized dogs, the prodromal sign of tetany was violent hyperpnea

Before considering the factor of alkalosis in these experiments with epileptic patients, we must consider various other changes which might have a possible bearing on the occurrence of seizures following over-ventilation in epileptics These changes are decrease in intracranial pressure, accelerated blood flow through the brain with decreased oxygenation of its cells, certain changes in physical properties of the blood, and consequent on the alkalosis, a decreased oxygen supply to nervous tissues, and a shift in inorganic base from blood to tissues Decreased intracranial pressure in itself should not produce spells for,

as we saw when considering the spinal fluid, seizures are more frequently associated with an increased pressure. It is possible that changes in caliber of cerebral vessels, with consequent changes in blood flow and oxygenation of nerve cells may play a prominent part. Direct observations by Jacoby (1926) and Forbes and Wolff (1928) showing contraction of pial arteries with over-ventilation and alkalosis, are important. This is discussed more fully elsewhere.

Concerning other chemical changes in the blood, Pfeiffer, Standenath and Weeber (1926) investigated changes in the proteolytic titre of urine and of blood serum with relation to over-ventilation and seizures. They present the data obtained in the form of seven charts. These show that the proteolytic titre of blood remained fairly constant, whereas that of urine fluctuated violently. Usually the concentration of the proteolytic enzyme diminished during over-ventilation. The significance of this observation is not clear. Georgi (1925, a and b) studied the blood in a group of 44 patients and 10 normals on whom Foerster performed his over-ventilation test. Blood was taken before and at two and ten minute intervals after the test. Although Georgi says he made observations concerning speed of sedimentation of red cells, viscosity of the plasma, refraction and coagulability of the blood, alkali reserve and calcium content, he presents data only on the "colloid stability test". This is the degree of flocculation which appears after mixing various amounts of citrated plasma with 26 per cent sodium chloride solution. Data of these experiments are presented by means of 3 tables (1925a) and several inadequately labeled charts (1925b). We are, therefore, largely dependent on the author's own interpretation of his data. He states that blood obtained from 7 patients at the time of seizure and blood from normal persons during over-ventilation showed an increased degree of flocculation of the plasma. Georgi believes that this indicates a change in the colloidal condition of the plasma, and that if similar changes occurred in the cells of the brain, seizures might result. He differentiates between colloidal instability caused by protein and by ion changes and believes that endocrine disorders may play a part in the supposed changes in permeability of cell membranes. Most writers consider that an increased rate of floccula-

tion, as well as increased speed of sedimentation of red cells and increased concentration of fibrinogen, is indicative of increased protein destruction in the body. Georgi did not find that the speed of sedimentation of red cells paralleled the flocculation test and apparently on this basis gave the latter test a wider significance than it usually holds. In a latter publication (1926) he states that changes in ion concentration is the factor of specific significance. Kafka (1926) made similar observations in 5 patients. Data are clearly presented, but are too fragmentary to be of much value.

Concerning acid-base changes in the blood during over-ventilation persons with epilepsy, like normal subjects, develop alkalosis. Frisch and Fried (1926) measured changes in pH and  $\text{CO}_2$  content of blood before and after over-ventilation in 5 patients. They obtained the characteristic lowering of blood  $\text{CO}_2$  with a shift of blood pH toward the alkaline side. Because this demonstrated alkalosis did not result in seizures, they concluded that seizures are not related to changes in the pH of the blood. They suggest that a shift in calcium and chloride ions are more important, but present no data. As a result of the "blowing off" of  $\text{CO}_2$ , base substances leave the blood and enter the tissues.

In clinical observations now under way at the Thorndike Memorial Laboratory of the Boston City Hospital, we are endeavoring to pursue this subject farther. Our patient D. T., a girl of 14 who has 50 to 100 short clonic seizures daily, constantly has a characteristic seizure after about two minutes of over-ventilation. Records of her breathing during the test are shown in Figures 7 and 8. We found that when seizures occurred the  $\text{CO}_2$  content of the venous blood was but 4 or 5 volumes per cent less than before the test. Serum calcium, plasma chloride and sugar changed but little. The oxygen content of the venous blood was increased, due apparently to the increased speed of blood flow through the tissues. In this patient by means of a standard procedure, we were able to test the effect of various factors on the length of time required to induce a seizure. We found that it made little difference in the appearance-time of seizure whether she was tested on a "good day" when seizures were few or on a "bad day." They could be as easily elicited when she was free from seizure because

of a fat diet as under ordinary conditions. Inhalation of amyl nitrite had no appreciable effect. Injection of NaCl on one occasion seemed to shorten the convulsion time. In this patient we found that over-ventilation was not accompanied by seizure if she respired in a closed system in which the expired  $\text{CO}_2$  was not absorbed (fig 8). This demonstrates that seizures were not due to the effort of over-ventilating.

*Relation to oxygen supply.* Lennox (1928) has demonstrated what apparently has not been observed previously, viz., that in certain patients having frequent slight attacks, these can be induced by decreasing the oxygen content of the respired air. This is done by having the patient rebreathe, the expired  $\text{CO}_2$  being absorbed. If the tension of the oxygen is increased, (by placing a weight on the bell from which air is being breathed) it will require a lower percentage of oxygen to induce a spell than if the tension is reduced (by increasing the counter weight of the bell). Also he found that a degree of anoxemia sufficient to induce an attack would not do so if the respired air contained an increased percentage of  $\text{CO}_2$ . Patient D. T., if breathing room air, reacts to over-ventilation with a seizure in about two minutes. A combination of over-ventilation and anoxemia produces a reaction much more quickly. Such an observation is recorded in figure 7. After four minutes of quiet breathing, when the oxygen in the inspired air had been reduced to about 14 per cent, 9 deep expirations induced a seizure. Excess oxygen was admitted to the apparatus, after which it required 40 expirations to produce a seizure. After several minutes of quiet breathing, when the oxygen content has fallen to approximately 12 per cent, seizures again began, but ceased promptly when more oxygen was admitted. If the patient breathed oxygen in place of air, vigorous hyperpnea for as long as six minutes did not result in a seizure (fig 8). On the other hand, if she breathed an atmosphere containing less oxygen than room air, seizures would occur in less than a minute. The length of time required to induce a seizure was roughly proportional to the oxygen content of the inspired air.

Furthermore, as has been stated, anoxemia alone, without voluntary over-ventilation, was sufficient to induce seizures. One observation of this sort has been recorded in figure 5. Such observations were made repeatedly in this and other subjects. In our patient,

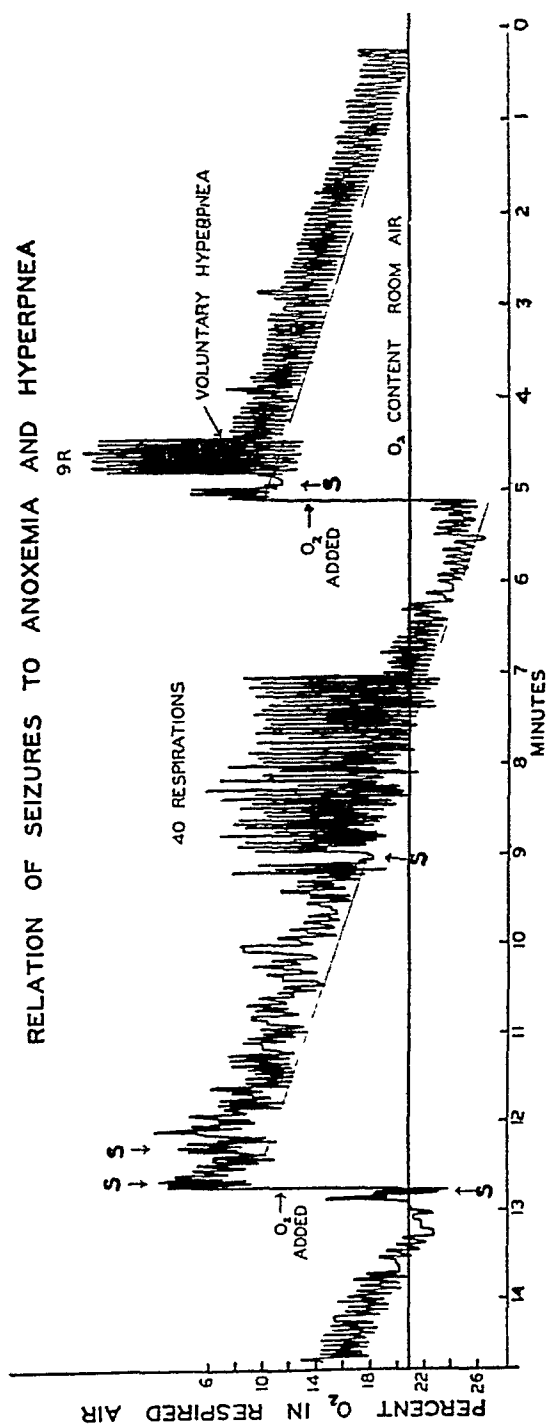


FIG 7 RELATION OF SEIZURES TO ANOXEMIA AND HYPERPNEA IN PATIENT D T

At the beginning of the period the bell of the Benedict-Roth metabolism apparatus was filled with room air. Ordinate marks approximate percentage of oxygen in the respired air. Abscissa marks minutes. S indicates seizures. Charts 7, 8 and 9 are one-third the size of the original.

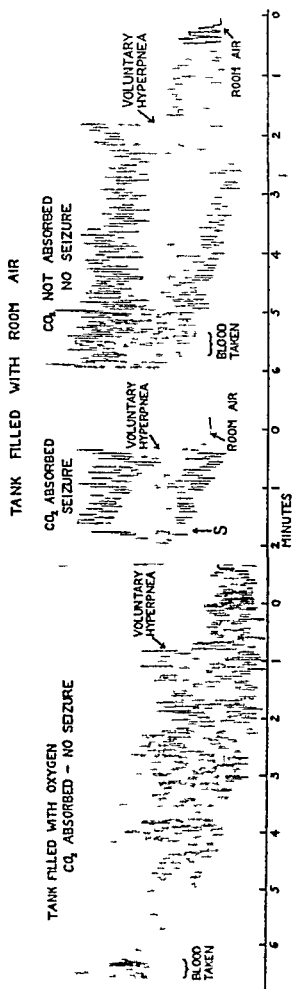


FIG. 8. COMPARISON OF THE EFFECT OF BREATHING OXYGEN RICH AND CARBON DIOXIDE RICH AIR IN PATIENT D. 1

In the center is the record of overventilation with the apparatus filled with room air, viz., a seizure occurred in 75 seconds. In the record on the right, the apparatus was filled with room air but the expired  $\text{CO}_2$  was not absorbed. Seizure did not result with 4 minutes of hyperventilation. In the record on the left—expired  $\text{CO}_2$  was absorbed, but the apparatus had been washed out and filled with oxygen. Seizure did not result even after nearly six minutes of overventilation. The measurements of blood gases will be presented in detail elsewhere.

C G, it required a greater degree of anoxemia to induce a seizure when acidosis was present. Patients having occasional grand mal attacks whom we tested did not react to hyperpnea and anoxemia with a convulsion.

That a deficient oxygen supply in normal persons is not sufficient to produce a seizure is shown by the experience of Schneider and Truesdale (1921) who performed 7000 such tests in aviation recruits. About half of the subjects became unconscious and some showed rigidity of muscles with occasional muscular twitchings. The average subject lost consciousness when oxygen content of the respired air reached 7 or 8 per cent. This is a lower level than our subjects reached before seizures occurred. Schneider found that the person who did not faint increased his pulmonary ventilation, his blood pressure and heart rate to compensate for the anoxemia. It will be of value to determine what physiological response epileptic patients make to oxygen lack. Though our patients (see fig 5) have a marked degree of oxygen unsaturation in the venous blood at the end of the test, the amount of oxygen consumed by the body does not always diminish as seizure impends. Observations of the gaseous content of arterial and of internal jugular blood which we are making should throw additional light on the factor of anoxemia with relation to seizures.

In these patients, having very frequent slight seizures we have demonstrated that a combination of anoxemia and hyperpnea is more effective in inducing seizure than either alone. This is understandable, for the two conditions supplement each other. In alkalosis the blood gives up oxygen less readily with consequent oxygen impoverishment of the tissues. It is possible, as we have suggested previously, that oxygen lack rather than alkalosis is the immediate cause of seizure.

It will be important to know if an induced convulsion will prevent the occurrence of a spontaneous convulsion. It should be stated that the observations made by us with reference to the production of seizures were carried out with the consent and full cooperation of the patients concerned. Obviously, a knowledge of the physiological factors which will produce seizures is an important step towards a knowledge of the procedures which will prevent them. Again, given a patient having convulsions at fairly regular intervals

which are not amenable to treatment, and given a safe and simple method for inducing seizures, it is possible that a convulsion precipitated under controlled conditions might save the patient from the approaching spontaneous convulsions under embarrassing or dangerous conditions

Whatever the chain of circumstances involved, the previously mentioned observations show that the irritability of nerves to the galvanic current is increased by over-ventilation. Contribution from a fresh source has been made by Bourguignon, Turpin and Guillaumin (1925) who, working with normal subjects, have shown that in over-ventilation, along with the alkalosis, there is a parallel variation in the chronaxie of nerves

*Summary* Alkalosis induced in epileptics by the administration of alkali or by over-ventilation may be followed by seizures. It is probable that anoxemia and possibly other related chemical changes in nervous tissues play a part in inducing seizures

#### *Effect of induced acidosis*

*Rebreathing* If seizures can be induced by over-ventilation, can they be stopped by the opposite condition, viz., rebreathing? We have been able to demonstrate this. One day our patient, D. T., was having clonic seizures regularly at intervals of about 45 seconds. She was attached to a Benedict-Roth metabolism machine, from which the soda lime was removed, so that she breathed an increasing concentration of  $\text{CO}_2$ . As seen in fig. 9, the convulsions were replaced by transient loss of consciousness, and then ceased. When she again was allowed to breathe room air, seizures returned at their usual frequency. We have found, also, that over-ventilation will not produce a seizure if the respired air contains a high per cent of  $\text{CO}_2$ . This observation checks with those of Fitz (1926) and Sheldon (1927). They found that attacks of muscle cramp and of hiccup, respectively, could be stopped by rebreathing. The important question of what stops a seizure has received little attention in the literature. In view of the demonstration that a high concentration of  $\text{CO}_2$  in the respired air may prevent seizures, it seems probable that accumulation of  $\text{CO}_2$  in the nervous tissues, as a result of stasis induced in the tonic phase of the convulsion, may play a part in stop-



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which are not amenable to treatment, and given a safe and simple method for inducing seizures, it is possible that a convulsion precipitated under controlled conditions might save the patient from the approaching spontaneous convulsions under embarrassing or dangerous conditions

Whatever the chain of circumstances involved, the previously mentioned observations show that the irritability of nerves to the galvanic current is increased by over-ventilation. Contribution from a fresh source has been made by Bourguignon, Turpin and Guillemin (1925) who, working with normal subjects, have shown that in over-ventilation, along with the alkalosis, there is a parallel variation in the chronaxie of nerves

*Summary* Alkalosis induced in epileptics by the administration of alkali or by over-ventilation may be followed by seizures. It is probable that anoxemia and possibly other related chemical changes in nervous tissues play a part in inducing seizures

#### *Effect of induced acidosis*

*Rebreathing* If seizures can be induced by over-ventilation, can they be stopped by the opposite condition, viz, rebreathing? We have been able to demonstrate this. One day our patient, D. T., was having clonic seizures regularly at intervals of about 45 seconds. She was attached to a Benedict-Roth metabolism machine, from which the soda lime was removed, so that she breathed an increasing concentration of  $\text{CO}_2$ . As seen in fig 9, the convulsions were replaced by transient loss of consciousness, and then ceased. When she again was allowed to breathe room air, seizures returned at their usual frequency. We have found, also, that over-ventilation will not produce a seizure if the respired air contains a high per cent of  $\text{CO}_2$ . This observation checks with those of Fitz (1926) and Sheldon (1927). They found that attacks of muscle cramp and of hiccups, respectively, could be stopped by rebreathing. The important question of what stops a seizure has received little attention in the literature. In view of the demonstration that a high concentration of  $\text{CO}_2$  in the respired air may prevent seizures, it seems probable that accumulation of  $\text{CO}_2$  in the nervous tissues, as a result of acidosis induced in the tonic phase of the convulsion, may play a

C G, it required a greater degree of anoxemia to induce a seizure when acidosis was present. Patients having occasional grand mal attacks whom we tested did not react to hyperpnea and anoxemia with a convulsion.

That a deficient oxygen supply in normal persons is not sufficient to produce a seizure is shown by the experience of Schneider and Truesdale (1921) who performed 7000 such tests in aviation recruits. About half of the subjects became unconscious and some showed rigidity of muscles with occasional muscular twitchings. The average subject lost consciousness when oxygen content of the respired air reached 7 or 8 per cent. This is a lower level than our subjects reached before seizures occurred. Schneider found that the person who did not faint increased his pulmonary ventilation, his blood pressure and heart rate to compensate for the anoxemia. It will be of value to determine what physiological response epileptic patients make to oxygen lack. Though our patients (see fig 5) have a marked degree of oxygen unsaturation in the venous blood at the end of the test, the amount of oxygen consumed by the body does not always diminish as seizure impends. Observations of the gaseous content of arterial and of internal jugular blood which we are making should throw additional light on the factor of anoxemia with relation to seizures.

In these patients, having very frequent slight seizures we have demonstrated that a combination of anoxemia and hyperpnea is more effective in inducing seizure than either alone. This is understandable, for the two conditions supplement each other. In alkalosis the blood gives up oxygen less readily with consequent oxygen impoverishment of the tissues. It is possible, as we have suggested previously, that oxygen lack rather than alkalosis is the immediate cause of seizure.

It will be important to know if an induced convulsion will prevent the occurrence of a spontaneous convulsion. It should be stated that the observations made by us with reference to the production of seizures were carried out with the consent and full cooperation of the patients concerned. Obviously, a knowledge of the physiological factors which will produce seizures is an important step towards a knowledge of the procedures which will prevent them. Again, given a patient having convulsions at fairly regular intervals

which are not amenable to treatment, and given a safe and simple method for inducing seizures, it is possible that a convulsion precipitated under controlled conditions might save the patient from the approaching spontaneous convulsions under embarrassing or dangerous conditions

Whatever the chain of circumstances involved, the previously mentioned observations show that the irritability of nerves to the galvanic current is increased by over-ventilation. Contribution from a fresh source has been made by Bourguignon, Turpin and Guillaumin (1925) who, working with normal subjects, have shown that in over-ventilation, along with the alkalosis, there is a parallel variation in the chronaxie of nerves

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ping the fit For the seizures of petit mal or equivalents in which there is no generalized cyanosis, one must suppose a local condition in the brain

*Fasting* Fasting as a method of treating various disease conditions has been used for centuries We are told that such treatment of epilepsy was practised in New England 50 or 75 years ago Guelpha

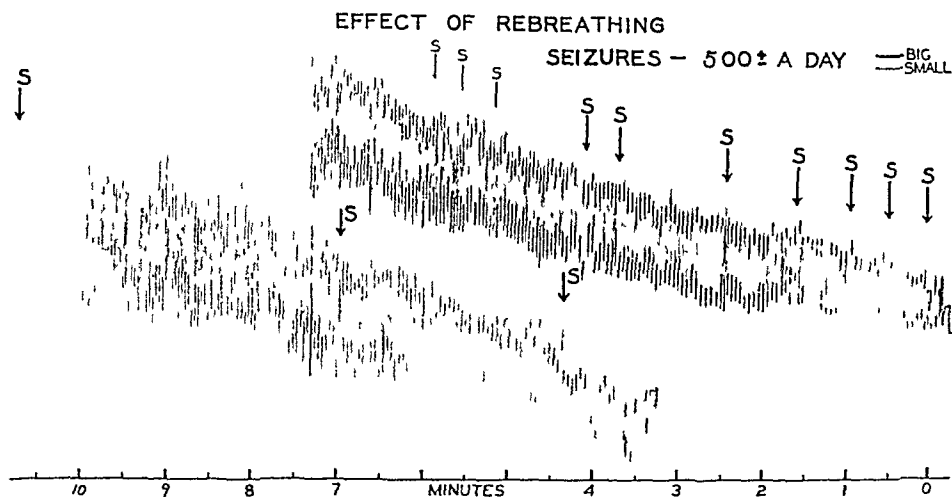


FIG 9 EFFECT OF REBREATHING ON SEIZURES PATIENT D T

Before the upper record was begun the patient for several hours had been having seizures at intervals of approximately 45 seconds The soda lime container was removed from the apparatus, so that expired  $\text{CO}_2$  was not absorbed Before the upper record was begun, oxygen was admitted to the apparatus A minute or two, in which the patient was released from the apparatus, elapsed between the two curves The heavy S indicates a characteristic myoclonic seizure and the light S a momentary loss of consciousness without convulsive movement After the patient was released from the apparatus and again breathed room air, seizures recurred at their previous rate of frequency

and Marie (1910) used 4-day fasting periods in 20 patients with inconclusive results Conklin, an osteopathic practitioner, has fasted hundreds of patients with epilepsy The one article which he has written (1922) gave a very favorable report,—the “cures” reaching 90 per cent in children and 50 per cent in adults This percentage, however, was based not on the total number treated but on the small proportion of patients whom the author had been able to follow Conklin has furnished us recently with case records of 127 epileptic patients whom he has fasted Unfortunately, the data are not com-



were fed a high fat diet without definite results Vollmer and Serebrijski (1926) fasted a boy of 6 for 3 days, with benefit Karger (1926) fasted 9 children, aged from 9 to 13 years for a period of from 6 to 12 days Lemonade in unnamed amounts was given them After the conclusion of fast, ketosis was maintained for as long as 3 weeks by a diet of cream, meat and eggs Of 10 fasting periods lasting from 5 to 8 days, improvement with respect to frequency of seizures was noted in all but two As soon as sugar was given and acetone disappeared from the urine, seizures returned The elimination of salt was without benefit Lennox and Cobb (1928) fasted 27 adolescent and adult patients, of the non-institutional type, who were mentally normal or nearly normal About one-half gave definite evidence of improvement during fast The most convincing results were seen in 6 patients having 5 or more seizures daily In 5 they ceased completely Following fast, in all but three or four of the patients, seizures recurred at approximately their prefasting frequency The notable exception was a woman having 2 to 3 convulsions daily of a focal origin (probably central nervous system syphilis) whose seizures disappeared with fasting and did not recur in the year following Some of their observations will be discussed in more detail presently

In contrast with these authors who have found seizures either absent or greatly decreased during fast, Weeks, Renner, Allen and Wishart (1923) reported no change in the number of seizures in a group of 64 patients whom they fasted for a period of 3 weeks An obvious possible explanation of these disappointing results is the fact that these patients were adult, confirmed, mentally deteriorated epileptics, a group notoriously resistant to any treatment The real reason for this resistance may be the circumstance that the degree of fasting ketosis obtained in these patients was slight What ketosis there was seemed to be associated with decreased frequency of seizures The group of 49 patients whose fasting was not complicated by use of previous diets had 908 convulsions in the 3 months period preceding fast Expressing this as 100, the proportionate number of seizures for the first week of fast was 122, the second week 59, the third week 100, and the 3 months following 106 Unfortunately, the authors

did not measure the plasma bicarbonate until after two weeks of fast. We know, however, that fasting acidosis is greatest during the second week, the period in which Week's patients had fewest seizures. Apparently these patients showed much less fasting acidosis than the patients of Bigwood (1924) or of Lennox, O'Connor and Bellinger (1926), in whom more definitely beneficial results were secured.

In patients having many seizures a day, the beneficial effect of fasting is so striking that immediately one asks for an explanation. Among the many and interrelated changes which take place in the body, one must not be too hasty in assigning a chief place to a single factor. Rest in bed, absence of material in the intestines, decrease of protein metabolism, decrease in salt intake, in basal metabolism, in intracranial pressure, in body water, and the presence of acidosis,—all have been named by various authors as the factors of importance.

Lennox and Cobb (unpublished data) have analyzed these various factors. Some of their patients maintained usual activity during fast, the presence of bran in the intestines and the feeding of salt apparently did not influence the number of seizures. Weeks et al (1923) obtained about the same results with fasting and with feeding bulky, non-nutritive material. Lennox, O'Connor and Bellinger (1926) and Talbot et al (1925) demonstrated that protein metabolism, as shown by the concentration of non-protein nitrogenous constituents in the blood, was not decreased. The relationship of some of these factors to seizures is shown in Fig 12. The heavy solid line indicating the daily number of attacks of petit mal does not parallel any of the others. As suggested by Geyelin, the most probable explanation of the improvement during fast is the accompanying acidosis, or closely related physico-chemical changes in the nerve cells. More detailed observations on this point will be presented later.

Concerning the therapeutic use of fasting, we believe that it may be useful in young patients having frequent convulsions, as a means of breaking up such seizures. We believe, however, that it is no more effective than a fat diet which produces a similar degree of acidosis, and it has obvious objections, in the discomfort to the patient and the limited time for which it can be employed. Moreover, in our experience patients may become temporarily psychotic during the fast.

*Fat diet.* If the beneficial effect of fasting is due to ketosis, the



consumption of a diet which is rich enough in fat and poor enough in carbohydrate to cause a ketosis of equal degree should be equally efficacious. Acting on the suggestion of Geyelin, Wilder (1921) and later Peterman (1924, a, b, 1925 and 1926) treated children by means of a ketogenic diet continued for long periods of time. Peterman gives his patients a gram per kilo of protein, enough total calories to equal 30 per cent more than their basal requirements and a ratio of calories from fat which is 2, 3 or 4 times the total calories from protein and carbohydrate. The ratio of fat to available carbohydrates is sufficiently high so that the urine gives a positive sodium nitro prusside test. Peterman's results so far have been very encouraging. Of 70 patients treated, 40 have been free of attacks for periods of from three months to three years, 18 have been greatly improved, 6 showed no improvement and 6 have been lost from observation. The best results have been obtained in patients with petit mal and in the younger children. Helmholz (1927) has given the latest summing up of these results at the Mayo Clinic. Of 91 children, adequately treated, 31 per cent have been made free of attacks and an additional 23 per cent were definitely improved.

Weeks, Allen, Renner, and Wishart (1923) for 48 days fed 6 institutional patients an extremely high fat diet (up to 580 grams of fat and only 4 of carbohydrate). Though the authors state that there was no effect on seizures, a tabulation of their data shows the following. If the number of convulsions before the diet be considered 100, the proportionate number during the period of fat feeding was 53, and after the diet 85. The fact that improvement was not more marked may perhaps be explained by the comparatively slight evidence of acidosis which these patients showed. The fact that patients with epilepsy are able to consume and utilize a diet so rich in fat may in itself be of significance. Dogs injected with ketone acids by Allen and Wishart (1923) gave evidence of intoxication, convulsions and death. He attributed this intoxication to some factor other than ketosis.

The rather meager observations of Schou and Teglbjoerg (1925), Vollmer and Serebrijski (1926) and Karger (1926) have been mentioned under fasting. Talbot, Metcalf and Moriarty (1927, a and b) presented charts of 2 children showing the absence of seizures in

the presence of ketosis and exhibiting the chemical changes in the blood of 14 patients and in the acetone excretion of 8 patients who were on a fat diet. Luther and Moriarty (personal communication) have had experience with 27 patients. A third of these have been free of seizures since undertaking the diet, 41 per cent were improved and 26 per cent not improved. Of the symptom-free group, all were under 13 years of age. These authors have observed no deleterious effect on growth, or on the general health of children in whom ketosis has been maintained for more than a year. McQuarrie and Keith (1927) have shown that, as one would expect, persons on a fat diet have least ketosis at periods farthest removed from a meal, viz., in the early morning. In our experience seizures are, however, not more frequent at that time. Patients having long continued ketosis need to be watched for possible production of arteriosclerosis, kidney irritation or weakening of bones through depletion of the inorganic base constituents.

Convulsions may occur in the presence of ketosis such as is present in diabetic coma (Labbé, 1920) and in the cyclic vomiting of children. As we shall show presently, seizures in epileptic patients may occur in spite of the presence of ketosis. In severe cases the presence of a reaction to sodium nitro prusside in the urine is not sufficient. There must be an actual increase in the pH of the blood.

Adults do not respond to treatment by acidosis, for one reason, because of the relative difficulty of maintaining acidosis in them. Children will develop ketosis on a much lower ketogenic, anti-ketogenic ratio than adults. In addition, for reasons which are unexplained but are possibly associated with the gradual development of the nervous system, children are more susceptible to various therapeutic measures. Another interesting circumstance is the adjustment to ketosis which the body is able to make. With the patient fasting or on a constant ketogenic diet, the plasma bicarbonate, which is at first decreased, gradually returns to normal, in spite of the presence of ketone bodies in both urine and plasma. This partly explains the fact that in severe cases, seizures return after an interval even when ketone bodies are present in the urine.

*Inorganic acidosis* It is important to know if acidosis produced by means other than by accumulation of  $\text{CO}_2$  and by ketosis is effective

in reducing the number of seizures. Uncompensated acidosis may be induced by the ingestion of acids such as HCl and H<sub>2</sub>SO<sub>4</sub> and of acid-forming salts, such as CaCl<sub>2</sub>, NH<sub>4</sub>Cl, MgSO<sub>4</sub>, NH<sub>4</sub>NO<sub>3</sub>, etc. The beneficial effect of such acidosis on tetany is well-known.

Bigwood (1924) gave HCl, as much as a liter a day of tenth normal, to several patients, with a reduction in seizures. Several writers have reported little or no benefit from ingestion of acid-forming salts, but

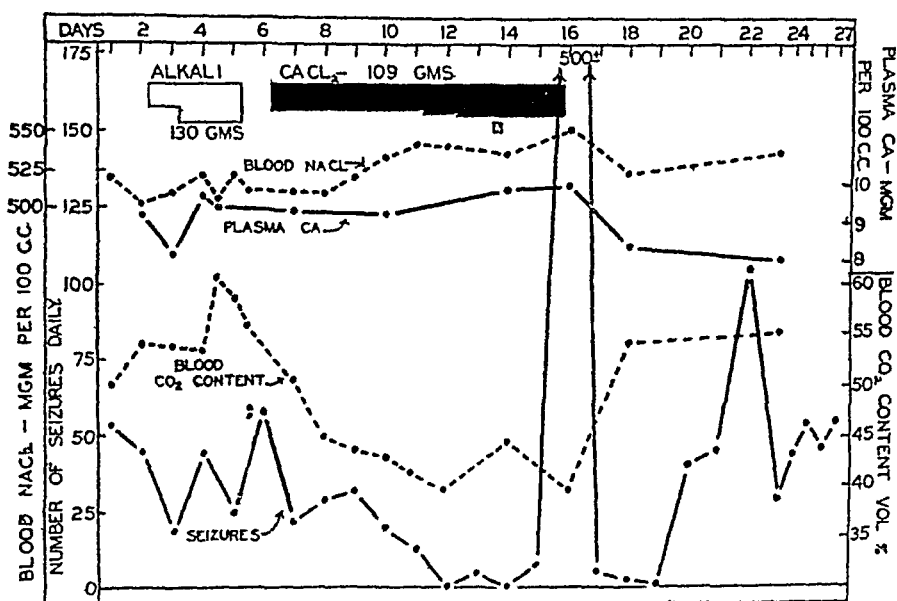


FIG. 10. TWENTY-SEVEN-DAY OBSERVATION PERIOD OF PATIENT D. T.

During three days alkali in the form of citrocarbonate was given without apparent effect on frequency of seizures. During 10 days 109 grams of CaCl<sub>2</sub> were given by mouth. Seizures were greatly reduced. On the tenth day, however, when there was still a marked acidosis, seizures recurred in very great frequency—approximately 500 in one day. Coincidentally the concentration of NaCl and calcium in the blood plasma was increased.

they did not determine whether acidosis was thereby induced. Some patients with epilepsy seem resistant to efforts to produce acidosis. For example, we fed one child, weighing 95 pounds, as much as 400 cc. a day of N/10 HCl without influencing either the reaction of the blood or the frequency of seizures.

Bigwood (1924) ascribed the beneficial results of potassium boro-tartrate, a drug advocated by Marie, Crouzon and Bouttier (1920), to the acidosis which it induced. However, Talbot, Metcalf and

Moriarty (1927b) when using this drug did not find significant changes in acid-base relations. Lennox and Wright (1926) believed that borotartrate was not as effective as luminal in controlling seizures.

Following the ingestion of  $\text{NH}_4\text{Cl}$ ,  $\text{CaCl}_2$  and  $\text{NH}_4\text{NO}_3$ , Lennox (1927) has obtained marked temporary reduction in the frequency of seizures (figs 10, 11 and 14). In a few instances in which the administration of these salts was continued, at the end of a week or ten days the patient went into a status of small seizures. One such series of observations is shown in figure 10. After preliminary trial with alkali, patient D T was given 10 to 15 grams a day of  $\text{CaCl}_2$ . The  $\text{CO}_2$  content of the blood and the frequency of seizures diminished. At the end of 10 days, however, when acidosis was still present, seizures returned in a flood, the patient having in the neighborhood of 500 in a day. This experience suggests that the increasing concentration of calcium or chloride in the tissues counterbalanced the beneficial effect of the change in pH. The fact that in feeding  $\text{NH}_4\text{NO}_3$  the acidosis is due to increase in blood chloride demonstrates the need for further study of this question.

Wilder (1921) suggested that the beneficial effect of fasting or fat diet was due to the anesthetic effect of aceto-acetic acid, which is closely related to ether. That this is not necessarily the case is shown by the fact that seizures may be inhibited by inorganic acidosis (ingestion of acids or acid-forming salts) and by rebreathing of  $\text{CO}_2$ . The following observation demonstrates this. Patient C G, having 10 to 12 petit mal daily, was placed on a constant ketogenic diet, on which she was free of attacks. The ingestion of 25 gms daily of alkali resulted in an increase of plasma bicarbonate, an increase of ketone bodies in the plasma and urine, and a return of seizures. On stopping alkali and feeding  $\text{NH}_4\text{NO}_3$ , ketosis decreased, plasma bicarbonate decreased and spells again disappeared. In this instance seizures ran parallel to plasma bicarbonate rather than to ketosis.

*Comparison of various procedures* In the usual patient with epilepsy, because of the variable interval between seizures, it is difficult to judge the effect of changes in acid-base relations. This is because in most patients such changes can be maintained for but a short time. For this reason, Lennox (1927) has selected patients who for a number

of years have had many seizures every day. In these patients any marked change in frequency of seizures would bear relation to experimental procedures instituted. Accompanying charts represent observation and treatment periods in three such patients. In these charts the solid lines represent the daily number of seizures and the dotted lines the plasma bicarbonate in volumes per cent of  $\text{CO}_2$ .

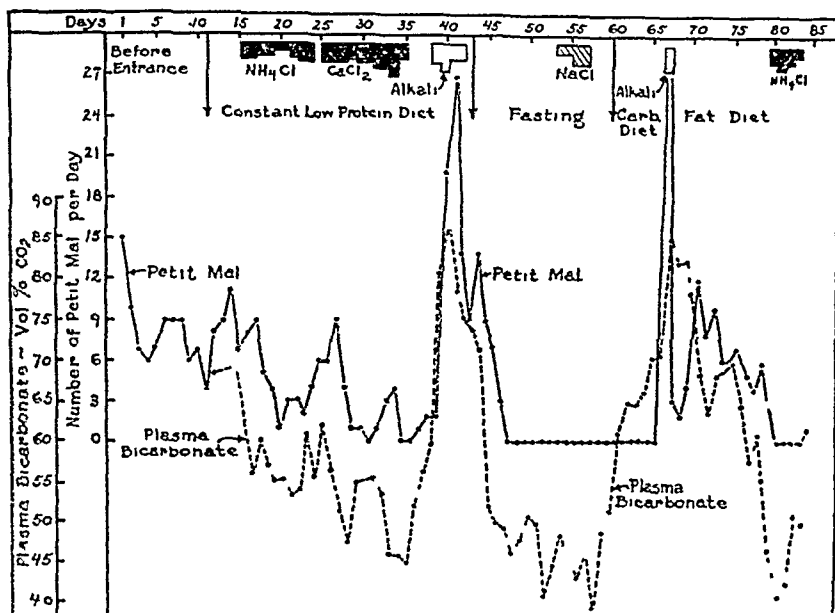


FIG 11 EIGHTY-FIVE-DAY OBSERVATION PERIOD OF PATIENT H G

The solid line represents daily number of petit mal and broken line plasma bicarbonate. Acidosis and alkalosis were induced at various intervals, as represented on the chart. In general the two curves followed a parallel course.

Patient H. G. (fig. 11), an intelligent girl of 17, has had from 5 to 20 petit mal daily for a number of years. Ammonium chloride was administered at the beginning of the period of observation with consequent acidosis and diminution in the frequency of seizures. Alkali was taken for 2 days with a great increase in seizures. The patient was then fasted for 16 days. Seizures entirely disappeared during this period and did not recur in spite of various procedures which might be expected to induce them, such as injection of adrenalin and administration of sodium chloride. She remained free of attacks for

a week after the resumption of a carbohydrate diet, in spite of the fact that the concentration of plasma bicarbonate had returned to normal. Several hours after the ingestion of 25 grams of alkali, however, seizures recurred with greater frequency than she had ever had them. When the patient was given a fat diet, and plasma bicarbonate had again fallen, seizures again disappeared.

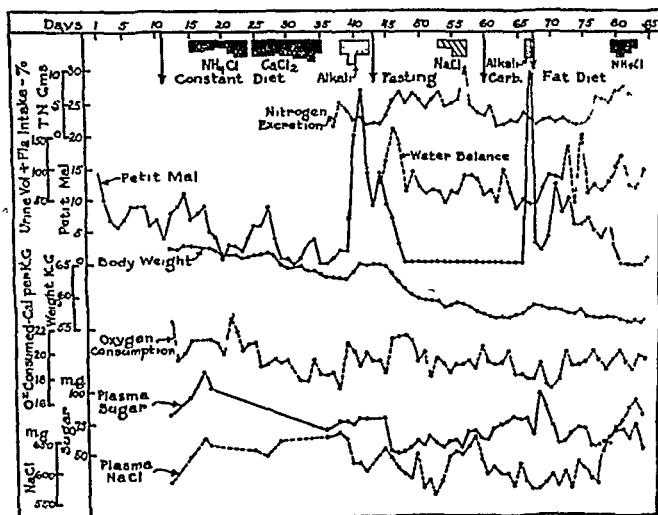


FIG. 12. EIGHTY FIVE DAY OBSERVATION PERIOD OF PATIENT H. G.

The upper solid line representing daily number of petit mal is the same as that shown in figure 11. Various observations, as noted on the chart, are plotted against this curve. None of these follow the curve of seizures as closely as does the curve of plasma bicarbonate, as shown in figure 11.

Figure 12 represents the same period of observation. In this figure, in addition to the curve representing the daily number of petit mal, we have charted various other daily measurements, viz, urinary nitrogen, excess of fluid intake over the volume of urine, weight, oxygen consumption, plasma NaCl and sugar. None of these measurements parallel the curve of seizures as does the concentration of plasma bicarbonate.

A second case is that of patient D T (fig 13), an intelligent girl of 13 who for six years has had from 20 to 100 clonic seizures daily. In a period of eighteen months these numbered 18,337. The greatest length of time which she could be kept without seizures on luminal was 11 days. Before the observation period shown in figure 13, she was having an especially hard time—seizures numbering up to 500 daily. On the fifth day of fast, seizures disappeared. For 16

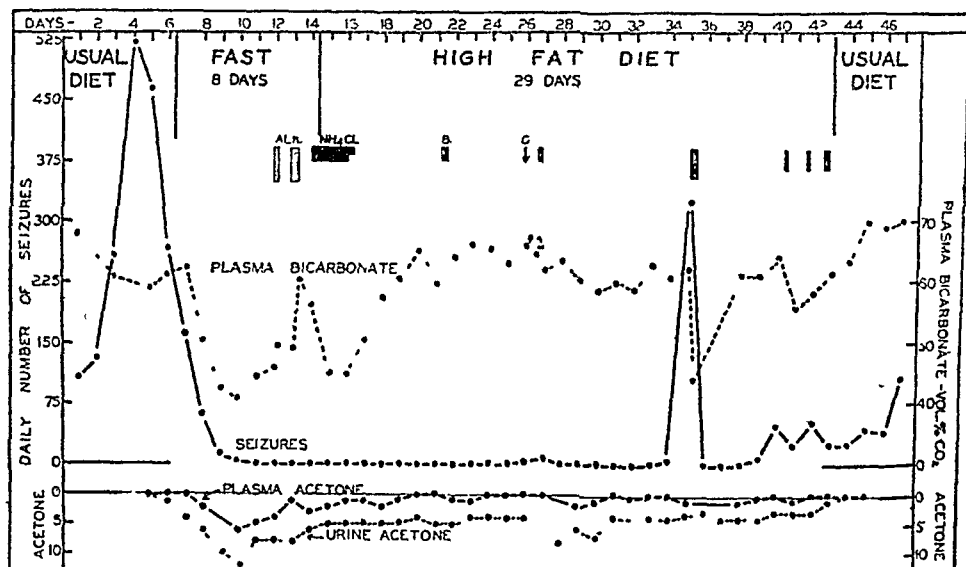


FIG 13 FORTY-EIGHT-DAY OBSERVATION PERIOD OF PATIENT D T

Solid and dotted lines at the bottom of the chart represent gradations in the strength of qualitative sodium nitroprusside reactions in plasma and urine. The patient was fasted for 8 days and ate a diet sufficiently high in fat to produce some ketosis for 29 days. Spells disappeared on the fifth day of fast. After 16 days without seizures the patient was given 60 grams of glucose for a blood sugar curve test, following which there was one seizure. A week later, in spite of the presence of ketosis, she had a status of petit mal. Following this, in spite of the diet, seizures returned but not with their previous frequency. In this period, though the urine gave a strong test for sodium nitroprusside, there was no acidosis, as measured by the concentration of bicarbonate in the plasma.

days (3 more of fast followed by a ketogenic diet) seizures were absent, except on one occasion when she was given 85 grams of glucose for a blood sugar curve test. On the twenty-ninth day of ketosis she had a status of small spells which disappeared a few hours after the ingestion of ammonium chloride. A few days after this seizures returned in moderate number, in spite of the fact that her urine gave a strong sodium nitroprusside reaction. In this patient ketosis was much

more effective than luminal in controlling seizures, and unlike luminal, its discontinuance was not accompanied by a tremendous increase in seizures

Patient L R (fig 14), an intelligent boy of 18 has had from 25 to 75 petit mal attacks a day with occasional grand mal for 10 years. Treatment by drugs and psychoanalysis had not influenced the frequency of seizures. In this patient during 15 days of fast, followed by 4 days of fat diet and periods in which calcium and ammonium chloride were given, the two curves representing daily seizures and

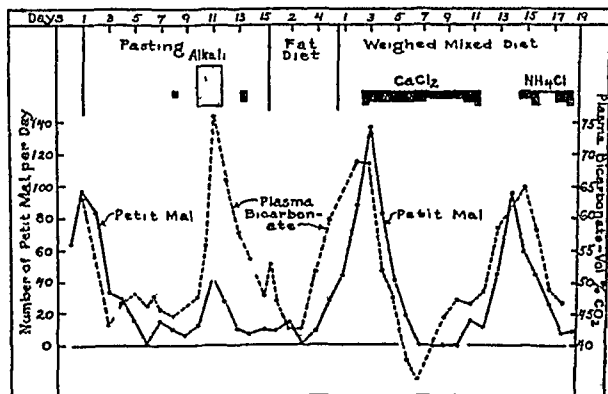


FIG 14 FORTY ONE DAY OBSERVATION PERIOD OF PATIENT L R.

He was given 15 days of fast, 5 days of fat diet, ten days of  $\text{CaCl}_2$  (10 to 15 grams a day) and 5 days of  $\text{NH}_4\text{Cl}$ . On the tenth and eleventh days of fast he took 125 grams of alkali (citrocarbonate)

plasma bicarbonate ran a nearly parallel course. In the midst of fasting he was given 125 grams of alkali with some increase in seizures. The striking thing in this chart is the fact that acidosis by means of acid-forming salts was as effective as fasting in causing decrease in the frequency of seizures. This medication, however, was continued for a few days only.

These and other observations which might be added make it plain that physico chemical changes that take place in the body profoundly



alter the frequency of seizures in certain patients. In the investigations which have been named, changes in acid-base relationships stand out most prominently because they are most easily measured. Obviously, however, this is not the only factor involved. On the induction of acidosis, seizures do not cease immediately nor do they return immediately after acidosis has been released. Therefore seizures are not a function of blood pH. We have direct observations also that anoxemia may play an equally important rôle. The best we can say at present is that, like tetany, epileptic seizures seem to be related to anoxemia, to alkalosis, and changes in the equilibrium of electrolytes of body (i.e., presumably nervous) tissue. Edema probably also plays a part.

It is important to ascertain whether this improvement in seizures, which occurs coincidentally with acidosis, is specific for seizures of unknown origin, the so-called essential epilepsy. Our evidence is against any such view. In the first place, as we have shown, the pH of the blood of patients with epilepsy is essentially normal. In the second place, in our experience young patients with the Jacksonian type of fit or with gross brain lesions have been benefitted also. In the third place, we have evidence that acidosis acts by causing a decrease in nervous irritability. During acidosis when seizures are reduced the tendon reflexes of patients are much less vigorous than they are normally. Our patient, D. T., has very active Chvostek's sign. When she is on a fat diet and the spells are absent this sign likewise is absent. Furthermore, Froehlich and Solé (1924) found in animals that the injection of acid decreased and of alkali increased reflex phenomena which were induced by the administration of strychnin and other convulsant drugs. We have mentioned the fact that accompanying the alkalosis of hyperpnea there is increased nervous irritability and a change in chronaxie.

If it is true that alkalosis increases and acidosis decreases nerve irritability, we would expect that this would have therapeutic implications for conditions other than epilepsy. The control of muscle cramp, tetany and hiccup by rebreathing has been mentioned. Wolff and Lennox (1928) have observed benefit from acidosis in a patient with post-encephalitic sequelae. We may hope that further study along this line will throw new light on therapeutics of other diseases in which there is abnormal muscle spasm.

Does ketosis merely dam the seizures in the organism, to be let out in a flood when treatment is stopped? Evidence on this point is not yet conclusive. We believe, however, that there is not a compensatory increase of seizures after a period of ketosis. It would seem that ketosis induced by a high fat diet offers the most practicable way of artificially controlling seizures. Unfortunately, it seems at present that only a small proportion of patients can hope for benefit from such diet. These favored ones are patients who are under 12 years of age, whose seizures are light and in whom the duration of the epilepsy has been short.

*Summary* Acidosis whether induced by rebreathing, by ketosis or by the administration of acid or acid-forming salts, in some patients causes a reduction in the number and severity of seizures. Continued use of the acid-forming salts,  $\text{CaCl}_2$  and  $\text{NH}_4\text{Cl}$  may be followed by a great increase in the number of seizures, due possibly to the accumulation of chloride in the tissues. The beneficial effect of acidosis is not due to changes in pH alone, but to related changes in the physico-chemical reactions of nerve cells, which results in a decreased irritability of the nerves. The observations have therapeutic implications for conditions other than epilepsy.

#### *Statistical considerations*

In any disease of unknown etiology, much can be learned from carefully gathered statistics. But with epilepsy, which is only a symptom, confusion is to be expected unless data are thoroughly digested. There are a number of interesting questions dealing with seizures concerning which we have insufficient facts.

*Distribution of patients* Davenport (1923) has gathered evidence concerning the distribution of epilepsy throughout the world. In countries in which reliable statistics are kept, there is apparently a fairly constant ratio to population.

*Distribution of seizures* The distribution of seizures by seasons, by months and by hours, and statistics concerning the age of onset, duration, recovery and mortality rates, etc., will be found in books and institutional reports.

*Relation of infantile convulsions to epilepsy* Patrick and Levy (1924) reviewed the literature and compared the after history of a

group of 752 unselected children with the histories of 500 epileptic patients seen in private practice. In the epileptic group, about 20 per cent had a history of early convulsions and in the unselected group about 4 per cent. In the epileptic group, patients whose seizures began in the first decade had a history of convulsions in infancy three times more frequently than patients whose seizures began in the third decade. Multiple early convulsions were more common in the epileptic and single convulsions in the non-epileptic group. Thom (1926) tabulated the after history of 265 patients who had convulsions prior to the fourth year, not associated with history of organic brain disease. Thirteen per cent of these continued to have convulsions and 16 per cent showed mental deterioration. The incidence of mental deficiency or epilepsy was almost twice as great in those cases in which there was no apparent exciting cause for the first convulsion.

*Heredity.* The question of heredity in epilepsy, in spite of its practical importance and the attention given it, is still a point of controversy. As Stuber (1921) points out, no conclusion can be drawn from the literature because of the lack of a unified plan in the collection of data, and because many of the groups studied have been institutional cases. It is quite possible that the inheritance in such a group of deteriorated, dependent individuals is quite different from that seen in private practice. He gives two pages of references to the literature. Burr (1922) through a study of 1449 cases, does not believe direct inheritance is important but that convulsions may be an evidence of congenital instability of the germ cell. The predisposition to nervous disease is inherited, but the specific disease which results is dependent on external causes. Myerson (1925) decided that a hereditary factor in epilepsy has not been proven. The constitutional factor may arise *de novo* in the lifetime of the individual himself, from his uterine existence onward. Brain (1926) has made an attempt to control his small series of 200 patients with a control series from non-epileptic cases attending the Nerve Department of the hospital. A family history of convulsions was present in 28 per cent of patients as compared with 10 per cent of the control series. In any such comparison, however, one must remember that patients having convulsions are likely to know more about similar cases in the family than patients who are not having convulsions.

*Relation to migraine* The close relationship between the occurrence of epilepsy and migraine has been noticed for many years. Indeed, many authors believe that migraine attacks are but sensory seizures. See Gowers (1906) and Krsch (1925). In 500 patients with migraine, Flatau (1912) found 7 per cent and Ulrich (1912) 12 per cent who had epilepsy. Buchanan (1923) in 128 cases of epilepsy found 54 per cent who had migraine. Psychologists do not insist on a migraine personality. It will be of interest to know if induction of acidosis is of benefit to patients with migraine.

*Constitutional types* The study of constitutional types with reference to disease processes in man is a subject the value of which has not yet been completely worked out. Benedict (1915), Buscaino (1922), Hoffman (1924), Reichardt (1924), and Grundler (1926) have discussed the constitutional type of epileptics. The last named author made measurements of 80 patients. He believes that epilepsy develops on the ground of schizothymic constitution. The group studied, however, was hardly large enough to justify the drawing of conclusions.

### *Practical considerations*

*Examination of patient with seizures* It is evident from all that has gone before that we must consider seizures as a symptom only. The first duty of the physician towards this, as towards any presenting symptom such as headache or abdominal pain, is to look for possible immediate and contributing causes. The fact that these causes may be obscure is the more reason for painstaking search. Whenever circumstances permit, patients should have the routine examinations outlined below.

Of first importance is a detailed history. The beginnings of life require careful attention. According to Ford (1926), two or three per cent of the cases of epilepsy originate in birth injuries. Toerster (1926) emphasizes the fact that prolonged venous stasis at birth may induce epilepsy. Besides the usual medical history, the physician should have all the facts which throw light on the patient's physical, mental and emotional make-up. The description of the seizures in most cases should permit division into one of three classes, viz., hysteria, Jacksonian epilepsy and other types of seizures. Within

the last named group, seizures from many different causes may closely resemble one another. In the same patient from time to time, seizures may differ markedly. Therefore, we can recognize no particular characteristics of a seizure which permit subdivision of the group into "symptomatic" or "essential" sub-groups. The physical and neurological examinations should include inspection of the eye grounds and testing of the visual fields, detailed examination of the cranial nerves, and of the sensory and motor functions, abnormalities in posture and gait, estimation of the stability of the autonomic nervous system, etc.

Besides the routine examination of urine, blood and feces, the following data should be gathered: x-ray films of the skull for information concerning old fractures, the size and shape of the sella turcica, evidence of increased intracranial pressure, and foci of infection in teeth or sinuses, in patients whose posture is poor or who give a history of constipation or other disturbance of the digestive tract, an x-ray examination of the stomach and intestines following the ingestion of barium, measurements of the pressure of the spinal fluid and of the degree and promptness of response to jugular compression, measurements of pressure after removing 5, 10 and 15 cc in order to obtain evidence concerning the volume of cerebro-spinal fluid, examination of the fluid for the number of cells, the amount of total protein and the Wassermann and gold sol reactions, measurement of the basal metabolic rate and in cases suggesting endocrine disturbance, a blood sugar curve test. Abnormal findings may call for other special examinations. In only a minority of any group of patients whose presenting symptom is seizures, will such detailed examination show abnormalities that are presumably related in a causal way to the seizures. In only a small percentage of this minority can the observed pathology be corrected and patients relieved. For the sake of these few, however, such careful work as we have outlined is justified.

The golden opportunity in the treatment of epilepsy is in its beginning. Then the detection and correction of an exciting cause may remove the symptom. Later, when the convulsive reaction has become a habit, it may not. Too often the physician after hearing the story, takes refuge in the name "epilepsy," and does nothing but prescribe a sedative and wait. "He may outgrow it." "The

fits may stop with the completion of teething, with puberty, with marriage, with the menopause,"—or (one might add) with death. After the lapse of years, when the patient is ready to go to any lengths in securing help, complete examination and careful treatment may be useless. A brain tumor may have become inoperable, or an epileptic habit may have become established.

*Prophylaxis* A wider recognition of the elements which may contribute to seizures will partially prevent their development. Eugenics may be made to play a part in limiting the progeny, not necessarily of those having convulsions, but of those with congenital deficiencies of the brain or other stigmata of congenital nervous disorder. Much may be accomplished by better obstetrical practice in the reduction of birth trauma or prolonged asphyxia. In case of meningeal hemorrhage either in infants or adults, as Bagley (1927) and Munro (1927) have demonstrated, there should be repeated lumbar puncture or if drainage cannot be satisfactorily secured in this way, a decompressive operation. Of 48 infants who received non-fatal intracranial injuries at birth and were treated by Munro by means of repeated lumbar punctures, only 3 (6 per cent) later developed convulsions, and of these two had received inadequate drainage. Prevention of meningeal infection and of head trauma is important. Psychic trauma, "splinters in the mind" no less than splinters in the brain call for early treatment.

*Treatment* Surely patients with no other disease have grasped at so many different therapeutic straws. When Celsus saw epileptics drinking blood from the wounds of dying gladiators he exclaimed in effect "What a miserable disease that makes tolerable such a miserable remedy" van Wageningen (1923). Many modern "cures" are not less miserable. Various therapeutic measures, both logical and empirical, have been detailed in the preceding pages. Here we shall mention only the general measures applicable to all patients.

If the physical and laboratory examinations give evidence of abnormality, such as pathology of the central nervous system, disorder of the glands of internal secretion, or of the function of the gastrointestinal system, the presence of foci of infection, etc., specific treatment should be instituted, when treatment is possible. In addition every patient should receive careful attention with regard to general hygiene, diet and medication.

*Hygiene* With regard to mental hygiene, it is evident that patients with epilepsy, as with any physical limitation, should not center thought on the seizures, but whenever possible, should see themselves as useful members of society. If possible, they should not be sent to an institution for epileptics, unless they have approached the deteriorated mental level common in such institutions. Discouragement must not be mistaken for deterioration. They should be protected from emotional strain and excitement. Certain patients who may have had unusual emotional experiences that were related to the onset of seizures, should discuss these thoroughly with the physician who should explain such experiences to them.

With regard to physical hygiene, by proper work or exercise, by sufficient rest and sleep, and by good physical habits, the patient should be put in the best possible physical condition. The development of a robust physique is a step towards gaining the staple vaso-motor system which so many patients lack. In certain patients the correction of posture, the regulation of bowels, or the adjustment of the exercise-rest ratio, may be followed by cessation of seizures. The demonstration that breathing an oxygen poor atmosphere may induce seizures speaks for the importance of eliminating nasal obstructions or of increasing lung ventilation and intra-abdominal circulation by proper posture and physical exercises. The well known clinical dangers of over fatigue finds experimental confirmation in the observation by Barbour and Abel (1910) with frogs and by Aub and associates (1925) with leaded cats, that animals when exhausted were especially susceptible to convulsions. As a first defense against seizures, the patient needs assistance in securing a quiet mind in an abundantly healthy body. Though any such regulation of the life manifestly does not transform the whole abnormal pathology which lies behind the seizures, it may be the last straw which swings the balance to the side of no convulsion.

*Diet.* Concerning diet in epilepsy, Hippocrates had the following to say: "The conjurors, purificators, mountebanks and Charlatans . . . have instituted a mode of treatment . . . enforcing abstinence from baths and many articles of food . . . Of sea substances, the surmullet, the blacktail, the mullet and the eel, and of flesh, those of the goat, the stag, the sow and the dog, for these are

the kind of flesh which are aptest to disorder the bowels Of fowls, the cock, the turtle and the bustard and such others as are reckoned to be particularly strong, and of potherbs, mint, garlic and onions, for what is acrid does not agree with a weak person " This diet list has a familiar sound, both for the definiteness with which certain articles are excluded and for the empirical quality of the reasons given We must admit, however, that the ancient practitioners had as good a reason for their exclusions as many modern specialists For example, Clark (1926) among other things excludes oranges, grapefruit, raw apples, radishes and raw celery Presumably many clinicians exclude fresh fruits on the supposition that they are acid forming and that in epilepsy acidosis is to be guarded against, a double error Many physicians forbid eating of meat on pain of instant seizure We have seen children who were not allowed to take milk and eggs Patients, sometimes with the approval of their physician, stop the article of food which was eaten at the meal preceding a convulsion. Such strict one-sided diets find no justification in the evidence which we have been able to gather The food, of course, should be simple and nutritious and should be only enough to satisfy caloric requirements The exception to this statement is the use in young persons of a ketogenic diet This is indicated in children whose seizures are frequent enough to justify the hardship involved in following the diet

*Medication* Observations concerning the use of various different drugs have been mentioned in previous sections Here we shall deal only with the sedatives Of these, bromide long held first place If chloride intake was reduced, it was found that some of the ingested bromide replaced body chloride and was more effective in stopping seizures Ulrich (1927) for example, has had experience with several hundred patients in an epileptic colony in Switzerland For a period of 9 years in which patients received bromide treatment, the average number of seizures yearly per patient was 64 In the following five years patients received bromide, and a restricted but inconstant salt intake Seizures numbered 43 In the last 14 years they have received bromide with a restricted constant salt intake and seizures have numbered only 16 As an aid to this method of treatment, Wuth (1927) has devised a simplified method for the rough approximation



of the bromide content of the blood As stated elsewhere, this whole question of the relation of various ions to seizures needs more careful study At the present time phenobarbital (luminal) is the standard drug for controlling seizures It has largely displaced bromide because of the fact that it does not so greatly depress the mentality Recent reports are by Sands and Irving (1921), Grinker (1922), Maillard and Meignant (1923), Rohde (1923), Stuurman (1923), Fox (1927), and Darling (1923) The usual dose employed is  $1\frac{1}{2}$  grains a day Luminal sodium being more soluble can be given subcutaneously or intravenously It has been introduced in the subarachnoid space by Tomesco and Constantinesco (1922), Romer (1923), Ayala (1926), who injected it into the *cisterna magna*, and Patterson, Damon and Levi (1926) The evidence of meningeal irritation which these various authors have mentioned makes one feel that the therapeutic results were bought too dearly The last named authors found that intravenous injection of 5 grains of luminal sodium in 3 patients with status resulted in almost immediate cessation of seizures

In one of our patients having 15 to 20 seizures every day, a single intravenous injection of 10 grains of luminal-sodium completely suppressed seizures for a period of 4 days Following the injection, over-ventilation produced only a transient loss of consciousness, instead of the generalized clonic contractions which usually resulted The loss of consciousness would seem to be a more fundamental feature of a seizure than the more spectacular convulsion

In the treatment of status, drainage of spinal fluid and the intravenous injection of from 5 to 10 grains of luminal sodium, are the immediately effective measures Inhalation of a mixture of 10 per cent carbon dioxide and 90 per cent oxygen should be useful Patients in status may not be able to take nourishment The resulting fasting ketosis may be one factor making for recovery Administration, when possible, of butter, cream or oil, together with plenty of water, would assist in maintaining strength, and be as effective as fasting Magnesium sulphate by mouth in 50 per cent solution serves the triple purpose of reducing intracranial pressure, increasing acidosis and cleaning out the bowels

In some patients the use of sedative drugs apparently eliminates a certain proportion of the seizures. In others it seems to dam them up in the organism, to be released in a flood when the drug is discontinued or the body breaks away from the sedative's control. Such a case is described by Lennox and Wright (1927). A careful statistical study over a period of years of a group of non-institutional patients is needed, to determine the ultimate effect on seizures of sedative drugs.

### *General conclusions*

The material which has been presented is too diverse to permit concise recapitulation. We have endeavored to make a summarizing statement at the end of each section. Here we shall give in a general way our conception of what is known and what must be learned, concerning the symptom called epilepsy.

Although we have discussed the four main theories which have been advanced to explain the neurological mechanism involved in a fit (the so-called irritation, release, short circuit and explosive theories), to none have we been able to assign an exclusive position. Probably more than one of these mechanisms are usually involved. The explosive theory, which presumes a sudden alteration of physical or chemical relationships throughout the brain substance (for example, such as is induced by extreme hypoglycemia or anoxemia) offers the largest field for further research.

For practical purposes the important consideration is the cause of the seizure, rather than the mechanism by which it spreads, i e, what pulled the trigger rather than what happened after the trigger was pulled. Obviously, the answer to this question rests on a knowledge of the structure and the function of the brains and the bodies of representative groups of persons who are subject to seizures. Data on which to build such knowledge are inadequate. Much of the information which we have concerns only those patients confined in institutions, an unrepresentative and comparatively small group.

The majority of the brains of institutional patients show some structural lesion. Such lesions are from various causes (principally developmental defects, traumas, infections and vascular accidents), and are of various sorts. They include, in the brain substance,

of the bromide content of the blood As stated elsewhere, this whole question of the relation of various ions to seizures needs more careful study At the present time phenobarbital (luminal) is the standard drug for controlling seizures It has largely displaced bromide because of the fact that it does not so greatly depress the mentality Recent reports are by Sands and Irving (1921), Grinker (1922), Maillard and Meignant (1923), Rohde (1923), Stuurman (1923), Fox (1927), and Darling (1923) The usual dose employed is  $1\frac{1}{2}$  grains a day Luminal sodium being more soluble can be given subcutaneously or intravenously It has been introduced in the subarachnoid space by Tomesco and Constantinesco (1922), Romer (1923), Ayala (1926), who injected it into the cisterna magna, and Patterson, Damon and Levi (1926) The evidence of meningeal irritation which these various authors have mentioned makes one feel that the therapeutic results were bought too dearly The last named authors found that intravenous injection of 5 grains of luminal sodium in 3 patients with status resulted in almost immediate cessation of seizures

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cicatrices and areas of atrophy and softening, and of gliosis, in the coverings of the brain, inflammation and cyst formation, and in the ventricles, dilatation. Intracranial tumors are present in about 3 per cent of the cases. The microscopic changes like the gross lesions, are neither constant nor specific. Concerning many of these lesions, one is in doubt as to whether they are the cause or the result of seizures. We need more information concerning the brains of persons who were not institutional patients, particularly of those whose symptoms had existed for a short period only. It is probable that a much smaller proportion of the brains of such persons would show structural lesions.

Concerning abnormalities in the body elsewhere than in the brain, the most constant is the inconstancy of physiological processes. For example, there is variation from day to day in such measurements as pH of the blood, oxygen consumption, blood sugar curves, activity of reflexes, vasomotor reactions, leucocytic formula, excretion of ammonia, weight, and nitrogen balance.

In any large group of epileptic patients, many give evidence of instability of the sympathetic nervous system. In view of the demonstration that cerebral arteries are under vasomotor control, circulatory reactions in the skin (such as cyanosis of extremities, dermatographia, flushing, pallor, areas of vasoconstriction, etc.) which indicate vasomotor instability are important as suggesting analogous disturbances in the intracranial circulation. Many patients have poor posture—oftentimes with evidence of ptosis of the gastrointestinal tract. Such abnormalities might exert an unfavorable influence through disturbances in circulation or through undue muscular fatigue. Constipation, a common complaint, may assist in precipitating seizures. A few patients present evidence of disturbance of endocrine glands, usually in the direction of a diminished function of the pituitary or thyroid glands. Many patients present abnormalities, the significance of which, if any, is as yet undetermined. For example, in the spinal fluid there may be increase above normal of the amount, pressure and total protein content, in the blood plasma one may find increase in the fibrinogen and in the degree of flocculation, increase of lactic acid, and of antiproteolytic ferments. There may be evidence of hypersensitiveness, etc. There

are, in addition, bits of evidence which suggest fundamental disturbances of metabolism in epileptics. So far, these have done no more than point the need for more carefully controlled and specialized research than has yet been attempted. The painstaking accumulation of apparently unrelated facts must go on, until, like stones for a mosaic, they are sufficient in number to permit their assembly into a complete and intelligible design.

Because no constant structural lesions have been demonstrated in either brains or bodies of persons subject to seizures, and because in the presence of very obvious abnormalities, such as brain trauma or hypoglycemia, only a minority of patients so affected will have seizures, we believe that such abnormalities as have been described play only contributory rôles. A knowledge of the functional abnormalities of nervous tissue is essential for further progress.

The greatest recent advance in our knowledge of epilepsy is the demonstration that changes in physicochemical processes in the body, and presumably therefore in the brain, may profoundly modify seizures. In fact, so fast have we traveled that we have at last caught up with the Father of Medicine! Hippocrates, or one of his school, wrote a treatise on epilepsy, in which he endeavored to take the symptom out of the realm of the supernatural and explain it on a physiological basis. At the close of his argument he makes this striking statement, "but whoever is acquainted with such a change in men and can render a man humid and dry, hot and cold by regimen could also cure this disease—without minding purifications, spells and all other illiberal practices of a like kind." Only within the last year or two has the truth of Hippocrates' underlying thought been demonstrated. Paralleling his concept, but paraphrasing his words, we may say that "whoever is acquainted with physiology and can render a man acidotic, dehydrated and fully oxygenated could also repress this disease, without minding purification of narcissistic personalities, ritualistic empirical diets and all other illiberal practices of a like kind."

Table 3 is a résumé of some of the physiological conditions which in the preceding pages have been shown to modify seizures. The list is, of course, tentative and incomplete, for ground has only just been broken for this type of exploration. Certainly chemical con-

stituents other than those named, e g , Mg, K, and Na, presumably play a part. The evidence so far gathered indicates that in certain epileptics subject to frequent seizures, these may be precipitated by oxygen lack and by alkalosis, however induced, whereas seizures may be prevented by an increased oxygen tension in the tissues and by acidosis, however induced. Though oxygenation of tissue and acid-base relations each plays an individual rôle, they complement each other; e.g., acidosis lowers the oxygen dissociation curve and allows greater utilization of oxygen by the tissues, anoxemia results in relative alkalosis.

Linked with these two factors is that of the water balance of tissues. Acute acidosis is associated with dehydration, because of the need for increased excretion of base, whereas acute alkalosis is accompanied by edema. Presumably increased permeability of tissues is a corollary of edema. Other factors named in table 3 (chemical constituents and intracranial pressure), cannot be fitted into the picture so readily. They may play only a subsidiary or occasionally significant part. These various factors are intricate parts of a whole. One cannot now say which is of most importance. If, however, we were to hazard a two-word guess concerning the fundamental element in the precipitation of seizures in epilepsy, it would be "oxygen lack."

From the physiological point of view the blood not only is a part of the brain but joins the brain to the rest of the body. In the observations which have been cited the degree of general anoxemia or alkalosis induced was much greater than ever occurs spontaneously in epileptics. Therefore, one must assume physiological changes in the brain which are not reflected in the composition of the peripheral blood. Such local physiological changes might be precipitated by sudden alterations in the flow of blood through the brain.

In view of the facts which have been presented, a convulsion might have some such explanation as the following. We know that under sympathetic stimulation contraction of cerebral arteries occurs, and we may assume that in epilepsy such contraction may occur. Arterial spasm would lead to decreased blood flow in the capillaries. This might lead to deficient oxygenation and consequently alkalosis of the brain tissue. Under these conditions one might expect an

increased passage of fluid outward through the capillary walls, with resulting edema. Some or all of these factors (oxygen lack, alkalosis, edema, change in electrolyte equilibrium, increased intracranial pressure) might stimulate nerve cells to the point of discharge with resulting muscular spasm. Apnea and muscular contraction would result in a great accumulation of lactic acid and  $\text{CO}_2$  in the tissues, producing a condition of acidosis which would initiate a reversible reaction, leading to a better utilization of oxygen, a retoration of circulation and release of muscle spasm.

TABLE 3  
*Tentative list of physiological changes in the brain which may effect seizures*

	CONDITIONS WHICH MAY TEND TO	
	Prevent seizures	Precipitate seizures
Oxygen	Rich supply	Poor supply
Acid base equilibrium	Acidosis by means of fasting, fat diet	
	Ingestion of acids or acid forming salts	Alkalosis by means of ingestion of alkali
	Breathing high $\text{CO}_2$	Hyperpnea—"blowing off" $\text{CO}_2$
Chemical constituents	Low chloride (?)	High chloride (?)
	High calcium (tetany)	Low calcium (tetany)
		Hypoglycemia
Water balance	Dehydration	Edema
Permeability of tissues	Decreased	Increased
Intracranial pressure	Decreased	Increased
Intracranial circulation	Impaired	Unimpaired

It is obvious that further knowledge concerning the relation of the metabolism of the nerve to its function will greatly extend our understanding of the conditions which contribute to seizures. Possibly this will provide new methods of therapy. Bock and his associates (unpublished data) believe that the process of physical training permanently alters the metabolism of muscle tissue, making it more efficient. It is possible that one might alter the metabolism of nerve cells also. Though it is not convenient for patients to live under conditions of increased tension of oxygen or carbon dioxide, it is possible to maintain acidosis by means of a ketogenic diet for considerable



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periods of time This measure when used in children is often of distinct value That benefit persists for a period after the resumption of normal diet suggests a persisting change in the physiological processes in nervous tissue.

One wonders whether a more complete understanding of the action and interaction of these physicochemical forces may conceivably give us in the next few years a clear understanding of the pathological physiology of fits Probably it will not The physiological changes which we have mentioned (anoxemia, alkalosis, edema) are themselves only contributory factors They tend to induce seizures by increasing the irritability of nervous tissues, producing an effect which is not specific for epilepsy Induction of acidosis is a useful therapeutic measure not only in certain cases of epilepsy, but also in other paroxysmal manifestations, such as, muscle cramps, hiccough and tetany. Furthermore, the physiological changes mentioned will produce seizures only in those who are subject to seizures. Therefore, the important question yet remains, why, under a given stimulus, one person should have a seizure and another not

This "constitution," or variability in the manner of reaction to a certain stimulus, is a quality of living matter and is not peculiar to epilepsy. Though this variability is presumably related to the subtle chemistry of the cell, its elucidation is for the future. When this is accomplished the present mystery not only about individual susceptibility to seizures, but also about individual susceptibility to disease in general may be dispelled

As we have emphasized above, there is no constant anatomical lesion in epilepsy, and only a minority of patients with extensive cerebral pathology have fits We are forced then to postulate some unknown constitutional element This abnormal "convulsive capacity" is presumably present in some degree in each person with epilepsy To that degree each person, whether hysterical, eclamptic or suffering from cerebral trauma, tumor or gliosis is an "essential" epileptic The relative importance of this convulsive tendency must vary enormously in different persons and in the same person from time to time. Moreover, our meagre knowledge and crude methods do not permit us to measure this tendency We cannot estimate in any individual what proportion it is of the total influences making for

seizures Therefore, the clinical use of such a term as "idiopathic" or "essential" is misleading, and implies a knowledge of the patient which we do not and cannot possess

The encouraging feature is that, although the exact mechanism of seizures is unknown, much can be done to prevent and, in the early stages, to relieve them It is the duty of the physician to search out the various contributing or precipitating factors which, in the individual patient, may make for seizures Correction of these abnormalities may effect symptomatic cure Finally, no one can doubt that continued study and search will bring a better understanding and a more rational and effective treatment of this distressing symptom

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## POLYCYTHEMIA

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It is the chief purpose of this article to consider the disease erythremia or polycythemia vera with especial reference to the papers, clinical and experimental, which have appeared within the past few years, and more particularly since the publication of the excellent reviews of Parkes Weber and of Gaisbock. A number of these more recent publications have served to throw further light upon the etiology, the clinical course, and the treatment of this obscure malady. The first of the two monographs mentioned gives adequate attention to the English and American literature. No attempt will be made, therefore, to cover completely the older literature except in so far as it appears necessary to give a comprehensive understanding of the basis of present conceptions. In order, however, to obtain proper perspective for a discussion of the pathological and etiological factors involved in polycythemia vera, it will be necessary to consider shortly the group of polycythemias which, as it is generally agreed, appear to have a better understood basis in pathological physiology.

Polycythemia is usually defined as that condition in which there is an increased number of erythrocytes per unit of the circulating blood. It is important to bear in mind that although five million red blood cells per cubic millimeter is the average number usually present in normal adult blood, counts even up to six million in robust active young men are by no means very rare, are commonly unattended by any symptoms, and to all intents and purposes appear to be quite devoid of clinical significance.<sup>1</sup> It is also of importance to distinguish between

<sup>1</sup> I am informed that in the class in Clinical Microscopy at the Johns Hopkins Medical School, where stress is laid upon accurate blood counts on each individual student, it is not uncommon to find each year one or more men with high erythrocyte counts, but without any symptoms whatever. Two such cases have been studied by Dr. Heath and the writer in the past two years. Although entirely without symptoms, both men have



and Cannon The latter authors have studied the phenomenon in cats and state that it fails to occur after removal of the upper abdominal sympathetic strands and bilateral severance of the splanchnic nerves, or after section of the nerves to the spleen, or, finally, after removal of the latter organ

At the present time the most satisfactory classification of the polycythemia not due solely to redistribution or concentration of the circulating blood volume, appears to be (a) those attributable to a lowered oxygen tension in the circulating blood or tissues, and (b) those due to some other, frequently unknown cause, not directly a result of low oxygen tension in the blood or tissues The classical example of the first group is the polycythemia observed at the lowered partial pressure of oxygen found with reduced barometric pressure

The occurrence of polycythemia in man at high altitudes was first demonstrated, it seems, in 1889 in the Peruvian Andes by Viault at a mine at an altitude of 4392 meters He found erythrocyte counts of seven and one-half, and eight million cells, not only in natives, but in himself and in a fellow traveller as well, although his blood at Lima—almost at sea level—had contained but five million cells This observation, which has since been confirmed by numerous observers, and which has been the starting point for many studies of importance in respiratory physiology, was in reality a confirmation of the hypothesis already formulated by Paul Bert in 1878 as to the physiological consequences of low oxygen pressure Bert had subsequently shown (1882), that the blood of the Peruvian llama, living at high altitudes, has a very high oxygen capacity The explanation of Miescher, who formulated the theory that oxygen lack in the bone marrow produces an increased new formation of red blood cells, became widely accepted, although it had been early shown that even at rather low pressures nearly complete oxygen saturation of the circulating arterial blood appears to occur The blood supply to the bones, however, is unique, it was argued, because of the relatively small arteries and wide veins, and the velocity of the blood flow in the venous capillaries of the bones is accordingly very low If one may assume a very sluggish blood flow in the marrow, although practically nothing is known at present of the conditions of blood flow in that tissue, except that it is throughout in intact vessels (Drinker, Sabin), small differences in oxygen tension



an increase in the number of cells per unit volume, and an absolute increase in the total mass in circulation. The actual state of the circulating blood volume is very imperfectly known in many conditions of polycythemia.

Probably the most common example of an increase in the number of erythrocytes per unit of volume met with by the clinician is the temporary relative polycythemia due to losses of fluid from the body, which results in blood concentration. Such losses may be due to persistent vomiting, or to severe diarrhoea. Asiatic cholera furnishes a classical example of blood concentration due to the latter condition. Copious sweating and abnormally low fluid intake from many causes of course produce the same effect. The familiar clinical signs of dehydration, the moderate leucocytosis which may accompany it, and the rapid return of the erythrocyte count to normal when proper fluid intake is reestablished offer few difficulties in diagnosis.

The polycythemia which has been noted at the extremes of life—"polycythemia neonatorum" (Lippmann), which may reach as high as 6.9 millions (Hirschfeld), and the polycythemia of the senium (Hammer and Schlesinger, Naegeli) are so poorly defined that they hardly deserve extended comment. The same may be said of that reported to occur after heavy meals, during the premenstrual phase, during pregnancy, after menopause, and in hibernating mammals (Gaisbock, Naegeli, Hirschfeld). A further physiological type is that which appears to follow immediately upon vigorous exercise and which cannot be explained alone on the basis of relative blood concentration at the periphery, or as a result of sweating and excessive fluid loss through the lungs. The recent work of Barcroft and his co-workers upon the spleen, as a storehouse and reservoir for erythrocytes which contracts in response to various stimuli and throws a large mass of reserve cells rapidly into the circulation, has provided an explanation for this and other hitherto obscure observations upon the sudden increase of red cells in the peripheral blood observed under a number of circumstances. Such, for example, is the type of polycythemia described by Lamson and others as following emotional excitement, and recently examined in detail by Izquierdo

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definitely palpable spleens. We have also examined another man who has a persistent high red cell count, but without a palpable spleen. Lommel has reported somewhat similar observations and draws similar conclusions.

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might assume great significance. Animals when kept at high altitudes develop a polycythemia just as do men, and the bone marrow shows marked evidence of erythropoietic activity (Zuntz, Loewy, Muller and Caspari). They are also stated to have an increased blood volume. Jaquet and Suter observed striking increases in red cell count and hemoglobin in rabbits at Davos, at a rather low altitude (1560 m), and Lippmann has recently reported a 20 per cent increase in erythrocytes and hemoglobin in natives in the same locality, together with an increase in the total blood volume. A number of other observers appear to have established the occurrence of increased cell and hemoglobin concentration at altitudes as low as ten thousand feet or even less (Stammers at Johannesburg, six thousand feet). The present evidence indicates that hemoglobin and erythrocytes increase in about the same proportions, so that the color index is unchanged (Schneider). More recent carefully controlled studies by Dallwig, Kolls and Loevenhart, and by Campbell, on animals kept at normal barometric pressure but at low oxygen tensions have served to confirm many earlier observations, and to emphasize the rather striking proportionality which seems to exist in general between the degree of anoxemia produced and the degree of polycythemia which results. Nevertheless, it is important to emphasize the fact that many marked individual variations in response are always to be found. Such experiments further serve to demonstrate the fact that the increased haematopoietic activity is a consequence of low oxygen tension alone and not merely of low barometric pressure. The response of man to low oxygen tensions by means of gas chamber experiments and by rebreathing gas mixtures containing low oxygen percentages has, it would seem, been exhaustively studied, and nearly all observers find appreciable increases in hemoglobin and in erythrocyte concentration (Gregg, Lutz and Schneider). Kuhn, by means of a mask device with which he could produce an artificial diminution of oxygen tension in the lungs claimed to be able to produce a well marked increase in the number of red cells in the blood. This, however, could not be confirmed by others (Senator, Morawitz), and certainly can have very little therapeutic value. Bence claimed that inhalation of oxygen lowers the polyglobulia of high altitudes as well as that of heart disease of erythremia. This question will be further discussed later in con-

nection with erythremia. It need only be mentioned here that Bornstein claims to have produced anemia by means of increased atmospheric oxygen pressure, and that the recent experiments of Campbell appear to point in the same direction. The extremely variable individual biological response to changes in oxygen tension is stressed by many authors, especially Naegeli. It is of the greatest importance and probably goes far to explain much of the confusion evident in the literature.

There appear to be two stages in the production of the erythrocytosis resulting from exposure to high altitudes. One appears quite rapidly, unattended by evidence of new blood formation, as after a balloon ascension, (said to produce as much as 12 per cent increase), or among aviators (Erich Meyer and Seyderholm, Hirshlaff, Culpepper), or after suddenly lessened air pressure (Grawitz, Schaumann and Rosenquist, Durant and Fredericq, Strohl, Binet and Fournier, and many others). The other stage, which only appears after a sojourn of some days at low barometric pressures, is accompanied by evidence of erythroblastic activity in the circulating blood (Zuntz, Haldane, Barcroft). According to Forbes' careful studies with the Cerro de Pasco Expedition, the maximum reticulocyte count in man appears after about one week at high altitudes. The first stage now seems in all likelihood to be due primarily to the rapid extrusion of red cells into the circulation, especially from the spleen. It is of historical interest, at least, to note that Senator at one time considered the change to be due to increase in the size of the erythrocytes and that Naegeli explained the phenomenon as due to plasma loss in the tissues or to abnormal distribution of the erythrocytes in the skin capillaries.

That the effect of high altitudes upon the blood forming organs and upon the erythrocyte and hemoglobin concentration of the circulating blood is due to lowered oxygen tension alone, is a thesis which has been seriously questioned, however, by competent observers, and many other suggestions are to be found in the literature. Bürker, while he considered the principal factor to be lowered air pressure, was also inclined to ascribe a rôle to the effects of cold, light, and to the dryness of the air. Concentration due to increased water loss through various channels, rapid surface evaporation at high altitudes, abnormal distribution of the peripheral blood under the stimulus of strong sunlight, wind

and vasomotor influences have all been suggested (Grawitz, Sahli, von Limbeck and many others) The observations of Kestner are interesting and suggestive. It had previously been observed by several workers (Zuntz et al., Abderhalden) that animals rendered artificially anemic by bleeding or by phenyl hydrazine could be made to regenerate their blood much more rapidly at high altitudes than at normal levels This regeneration in anemic animals under low oxygen tension was indeed much more striking than the new blood formation ordinarily induced in normal animals Morawitz reports the same effect in human anemia and believes that a sojourn at high altitudes has an important therapeutic value Kestner repeated and confirmed this effect upon anemic animals in a low pressure chamber, but at the same time he found that an equal or even more striking change could be produced by direct radiation of the animal itself or by pumping into the animal chamber air which had been radiated by an arc lamp The effect of light in the production of polycythemia has been noted by others, as in persons who handle x-rays, radium and radioactive substances, etc. Blood volume studies in animals (Abderhalden) have indicated a decided increase coincident with the onset of polycythemia. The state of the blood volume has not yet been satisfactorily studied in man at high altitudes, but the indications are that it is increased (Barcroft et al, Douglas, Haldane, et al).

A further important group of polycythemas seem to be caused by cardiocirculatory abnormalities or by an obstructed gas exchange in the lungs This group is well recognized and the mechanism of its production has always been tacitly assumed to be similar to that produced by low oxygen tension, as at high altitudes. It includes conditions affecting normal pulmonary ventilation—emphysema, stenosis of the trachea or larynx (Vaquez, Sellier, Labbe), and compression of the thorax (Reckzah, case II), lung tumors, or tumors pressing on the lungs, the various masses producing mediastinal obstruction, gas poisoning by pulmonary irritants, and clinical (spontaneous or induced), or experimental pneumothorax, as well as chronic cirrhotic pulmonary phthisis (Gutzeit, Moog and Pelling, Durant and Fredericq). Fredericq's case observed during the war is especially interesting. It was that of a soldier with a total right

pneumothorax, seemingly well compensated, in which the erythrocyte count was eight million

The polycythemia of congenital heart disease is classically found in pulmonary stenosis. An interesting study of this phenomenon is that of Frommherz. From his report and that of others it is likely that an enlarged liver and spleen are not uncommon in this condition. It is of importance also that such pathological evidence as is available indicates that there is abnormal haemopoietic activity in the bone marrow with disappearance of the normal fatty tissue (Weil, Weber, Machey, Todtenhaupt). Weil's two cases, which are quite well described, were in young children. In one case the spleen was much enlarged. We have not found reports of examinations of the bone marrow in cases which have reached maturity, with the exception of Todtenhaupt's case, a young man of twenty-five. The erythrocyte count was 13.9 millions. Because of this extraordinary increase a venesection of 750 cc was done, which caused exsitus. The yellow bone marrow was completely changed into the red type, as in polycythemia vera. It is of interest that in this condition, where very high red counts have been reported and are certainly not uncommon, descriptions of cerebral thromboses or of hemiplegias, such as are so common in polycythemia vera, are rarely published. They nevertheless occur (Wright, H. L. H., cases<sup>2</sup>). Red cell counts of seven to eight and one half million are commonly found and several have been reported as high as ten million. We have not been able to find, curiously enough, any very carefully detailed studies of the morphology, or of other factors, chemical or physiological, of the blood in congenital heart disease. It would be of great interest to know in how far the condition of the blood resembles that found in polycythemia vera.

One group of cases of polycythemia of cardio pulmonary origin

<sup>1</sup> Dr F. R. Ford has very kindly drawn the writer's attention to two cases which have occurred in the Harnet Lane Home, Johns Hopkins Hospital. The first, a child of twelve (no. 47006) had a residual spastic hemiplegia which had appeared following convulsions during an attack of measles at the age of four. The child was markedly cyanosed with evidences of pulmonary stenosis, clubbing of the fingers, and erythrocyte count of 9.5 million and hemoglobin 125 per cent. Both liver and spleen were palpable.

The second case (no. 51175) was an infant of twenty months diagnosed as pulmonary stenosis and with paralyzed right arm and leg and clubbing of the fingers. The child died of pneumonia but there was no autopsy. The date at which the paralysis occurred could not be exactly determined.

has excited particular attention in the past few years. It seems to have been first described in 1901 by Professor Abel Ayerza of Buenos Aires, and was the subject of a medical thesis by Marty in 1909, (in which the term Ayerza's Disease, "cardiacos negros," was first used). Arrilaga has recently written an excellent monograph on the subject. A certain degree of confusion has crept into the various descriptions of this syndrome. The clinical picture is one of chronic cyanosis, of varying but often extreme degree, usually associated with pulmonary emphysema, and with evidence of dilatation and hypertrophy of the right heart, whose ventricular walls often become as thick as those of the left side. The patient often gives a history of attacks of asthma or bronchitis extending over many years and has marked dyspnoea on exertion. The cyanosis and the pulmonary symptoms may be of very long standing, as well as the dyspnoea, before evidences of heart failure appear. Secondary sclerosis of the pulmonary artery, often accompanied by dilatation, with obstruction to the circulation of blood through the lungs (the general circulation being left relatively intact), is the explanation usually given to these cases. Arrilaga, however, considers the disease of the pulmonary artery to be primary. Rogers has described this pulmonary sclerosis and dilatation and has ascribed it to a syphilitic basis. His pathological reports of cases in Bengal are unfortunately accompanied by very poor clinical descriptions and do not include reports on blood counts. Congenital narrowing or hypoplasia of the pulmonary artery may play a rôle in some cases, and in addition, emphysema, pleural adhesions, pulmonary fibrosis of chronic tuberculous origin (Gutzeit), or chronic interstitial changes are contributory to the condition. Weber lays stress on the frequency of the syndrome in East London among middle aged Hebrews. Syphilis and pulmonary arteriosclerosis are stressed by South American writers and Warthin's case showed syphilitic arteriosclerosis of the pulmonary arteries. Weber does not believe that syphilis is an essential factor in "cardiacos negros," and states that both of the new cases reported by Lucas in his paper on erythremia several years ago were in reality, cases of Ayerza's Disease, not of polycythemia vera. Clarke and others have very recently reported cases of primary disease of the pulmonary artery which were of congenital origin and they suggest that an inherited factor is present in

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many of them. There can be little doubt that a number of cases reported in the literature as polycythemia vera will fit very well into this somewhat ill defined group. Pulmonary arteriosclerosis appears to be relatively common in the tropics. The spleen is sometimes enlarged, sometimes tuberculous, there is usually dilatation and chronic passive congestion of the liver and sometimes clubbing of the fingers. The polycythemia in these cases may be very great, ranging as high as ten or eleven million cells per cubic millimeter. According to Morse, the picture is due to pulmonary fibrosis rather than disease of the pulmonary artery. The thickening of the pulmonary vessels recalls to mind the curious pulmonary arterial thickening observed by Campbell, and shown in illustrations in his recent article describing the effects on animals kept over long periods at low oxygen tensions. On the other hand, it is interesting to recall that in both of Schreyer's carefully described post mortem examinations in cases which seem to have been true polycythemia rubra, there was well marked widening of the pulmonary artery and thinning out of its wall. Nathan agrees with Escudero that there are probably two periods in the evolution of this syndrome: first, a bronchitic period, and second, a cardiac period which is first shown by evidences of galvanometric and radiographic preponderance of the left side of the heart. It seems fairly clear that no serious difficulty should ordinarily arise in the differential diagnosis of Ayerza's syndrome from that of polycythemia vera. In the former case, "cardiacos negros," a considerable arterial oxygen unsaturation must usually be present (we have not found studies reported), and the pulmonary and cardiac changes are fairly outspoken in definite cases.

So far as the polycythemia which may accompany heart disease is concerned aside from the special groups discussed above, it appears to be fairly well established that patients suffering from mitral lesions are more apt to have polycythemia than those with aortic lesions, and that increased blood counts are most apt to occur where emphysema exists or where secondary changes occur in the lungs, demonstrable either by physical examination or in the x-ray. Such polycythemias rarely exceed seven million cells. So far as the author is aware, minute studies of the morphology of the blood have not been made and little is known as to the alterations in the circulating blood volume in this



group of polycythemic conditions. Two isolated observations by W. Schmidt showed an increased blood volume. As Gutzeit has observed, many cases of serious heart disease with secondary lung changes show no increase in the blood count whatever. Factors other than the heart disease itself must be present in such secondary polycythemias.

A considerable number of chemical agents and pharmacologically active substances are said to produce polycythemia. Most of them have been summarized by Lamson. Only a few will be alluded to here. Arsenic, and particularly phosphorus, have long been recognized as inducing polycythemia, but the exact method by which they cause bone marrow stimulation is not known. The polycythemia associated with phosphorus poisoning may be very considerable. Thus out of 118 cases observed at Prague, 44 showed counts between 5 and 6 million, 20 between 6 and 7 million, 11 between 7 and 8 million; and 3 exceeded 8 million (Silbermann, v Jaksch). Among the metals it is mentioned in experimental manganese poisoning, and it has even been suggested that polycythemia may be due to disturbed (increased) cell respiration due to the presence of abnormal amounts of iron or manganese as an oxidation catalyzer<sup>1</sup> (Schreyer). Persons exposed to mercury and to iron and those dealing with radium salts are reported to be subject to polycythemia. Recently reported studies by G. L. Muller have shown that an extremely powerful agent in the experimental production of polycythemia, normoblastosis, and erythrocytic hyperplasia of the bone marrow is to be found in gum shellac. An excellent discussion of the question with literature is given in her article.

Carbon monoxide poisoning produces polycythemia in the experimental animal, as was early shown by Nasmith and Graham. The polycythemia occurring in chronic carbon monoxide poisoning in man appears to be recognized as an established fact. It is not of so regular occurrence in acute poisoning. The case of cantharides poisoning with polycythemia reported by Lipsitz, Fuerth and Cross was supported by interesting experimental studies. It is widely stated that in the polycythemias induced by poisons the hemoglobin is usually reduced, although the number of cells is increased.

A number of infectious diseases have been stated to produce poly-

cythemia It is very probable that this is frequently only a dehydration phenomenon, excessive amounts of moisture being evaporated off due to the increased metabolism The mechanism is probably similar in the polycythemiae from time to time reported in diabetes insipidus and in diabetic coma In the latter condition an actual diminution in the circulating blood volume has been reported (Chang and Harrop, also, Eppinger and Schurmeyer, and Detre) On the other hand Weber thinks that there is a polycythemia typical of obsolete or quiescent pulmonary tuberculosis which may be compensatory to fibrotic changes in the lungs, again a question of interference with adequate pulmonary oxygen exchange

The polycythemia produced by adrenalin is fully described by Lamson A more recent study is that of Edmunds and Nelson The reader must be referred to the earlier monographs for the literature on its production by tuberculin, by the injection of serum from anemic animals, and other experimental procedures

Hamilton records an investigation by G R Minot in 1918 upon a group of girls suffering from ether poisoning in the manufacture of smokeless powder A considerable number had polycythemia, up to 7.8 million Kilgore has recently reported the occurrence of polycythemia, strikingly resembling polycythemia vera, in two persons exposed to aniline dye fumes as dyers of feathers One of these had indeed been previously reported as a case of polycythemia vera, greatly improved with x-ray and benzol (Hurwitz and Falconer) It is frequently stated that polycythemia may follow the methemoglobinemia produced by nitrites and aniline dye products It is also produced by toluyldiamine, nitrobenzol, and atoxyl The question of its occurrence as an over response to the stimulation of hemorrhage is very interesting It is reported in hemophilia (Pick), paroxysmal hemoglobinuria (Pels), scurvy, and hemolytic icterus

Talquist discusses the occurrence of erythrocytosis in chronic alcoholism The polycythemiae of gas poisoning and of shock are no doubt largely due both to a redistribution of blood into the peripheral vessels and to abnormal diffusion of fluids into the tissues, as well as to interference with pulmonary gas exchange

The polycythemia reported by Schulmann and Weismann associated with congenital syphilis, in which the erythrocyte count dropped

from twelve million to less than six million after neo-arsphenamine treatments, and the polycythemia described by Pribram in a patient with multiple tumors of the bone marrow and Bence-Jones proteinuria, are recent examples of cases which seem to be secondary to some well defined cause

The striking thing with regard to all of the so-called "secondary" polycythemias is their many points of similarity and contact with polycythemia vera. The trend of many articles in recent years has certainly been to emphasize this close relationship still further

#### POLYCYTHEMIA VERA

The first mention of the clinical syndrome chronic cyanosis, splenomegaly, and polycythemia appears to have been made by Vaquez in 1892. He first considered it as probably due to a form of congenital heart disease, but he later disproved this at autopsy. About a dozen or more cases were then reported in the French, English and American literature, but general attention was first drawn to the new "clinical entity," at least in England and America, by the appearance of Osler's papers in 1903 and 1904. The striking appearance of the patients, and the problem of the relationship of the syndrome to other polycythemias, produced by better understood alterations of physiology, no doubt explain the great interest displayed in the disease since that time. Thus Lucas in 1912 was able to find records of 179 cases and the number has much more than doubled since that time. It can no longer be regarded as a very rare disease, although it is usually so considered in the text-books. A number of synonyms have been proposed for the condition, of which Polycythemia Vera, Erythremia,<sup>3</sup> Splenomegalic Polycythemia, Myelopathic Polycythemia, Polycythemia Rubra, Polycythemia with Chronic Cyanosis, Erythrocytosis Megalosplenica, Vaquez's Disease, and Osler's Disease are probably the best known.

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of onset, as is well known, is usually in middle or late middle life, but evidences of the condition are frequently recognizable at a much earlier period. Patients are usually very vague in their statements concerning the exact date when their symptoms commenced. It is evident that the disease, erythremia, or rather an erythrocytosis which precedes it, is likely to have been present for a long time before it finally obtrudes itself upon the consciousness of the patient. Cases are cited of individuals who have applied to their physician for cosmetic reasons, to be rid of the unnatural red flush of the skin—"mehr rot als krank"—and who are otherwise symptom free. Others may apply for aid on account of the splenic tumor, but who have had, even on careful questioning, very few if any other disturbing symptoms. The decades during which the malady appears are just those in which the development of secondary lung changes, fibrosis or emphysema, or of arteriosclerotic changes in the brain, may be the culminating event which finally impresses on the mind of the sufferer the consciousness of a serious disorder. Nervous symptoms are among the most common for which medical advice is at first sought, and, it may be noted, typically those symptoms which are common in mild grades of chronic anoxemia. There does seem to be a certain rather characteristic type of body build in persons suffering from this disease, a fact which has been remarked by several authors. They are very seldom stout or overweight, but on the contrary are usually spare, with thin, often rather narrow faces. From the records available of our cases at this hospital, persons of fair complexion are more frequently affected than are brunettes, a point of similarity to pernicious anemia.

#### THE SKIN AND MUCOUS MEMBRANES

The striking color of the skin in polycythemia vera and the various factors in its production have been the subject of interesting studies. It was originally described by Vaquez as a cyanosis, but of "*une forme spéciale*," and the distinction between the color typical of polycythemia and that of ordinary cyanosis has really always been well recognized by writers. The primary cause of cyanosis, as due to the color of the blood itself when an abnormally large proportion of reduced hemoglobin is present has been extensively studied by Lundsgaard, and later by Lundsgaard and Van Slyke in their excellent monograph

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It is quite evident, however, (as indeed these authors have pointed out), that cyanosis in general and especially the peculiar color seen in polycythemia are very much affected by other factors. Chief among these are the thickness and amount of pigmentation of the skin, the number, distribution and state of dilatation of the peripheral capillaries and venules, and the rate of capillary blood flow.<sup>4</sup> As will be pointed out later, the extraordinary increase in the blood volume, which in typical cases seems to fill the vascular tree to its fullest capacity, is of prime importance and probably constitutes a most significant pathological alteration in this disease from the standpoint of its symptomatology. It is nowhere more marked than in the minute skin vessels, which have been particularly studied by Brown and his co-workers. These capillaries are engorged and distended to capacity, and there is marked slowing of the blood flow. This delayed, sluggish peripheral circulation no doubt accounts for the sensitiveness to cold of which these patients often complain, and probably for the lowered body temperature frequently described (Hirschfeld). Nearly always they do better in a mild or warm climate. Excessive sweating, especially of the palms and soles, is often complained of, but this may also be in part due to the increased basal metabolism.

The distribution of the abnormal skin color is of interest. It occurs especially on exposed surfaces—the face, particularly the cheeks, the tip of the nose, and the ears are usually prominent. Sometimes it extends to the neck, but the trunk in general shows no such remarkable color change. The hands and dorsal surfaces of the forearms are colored, but less often the lower legs and feet. At times, however, especially in patients with erythromelalgic symptoms, the coloration of the lower extremities is very striking. It is a mixture of blue and red, the shades depending, as Osler early recognized, upon the state of dilatation of the peripheral vascular network and upon the speed of the circulation through these areas. One recalls his vivid description of the patient whose color in hot weather was “red as a rose” but in winter as “blue as indigo.” The facial color has been compared by various writers to that of blushing or to the appearance after exposure

<sup>4</sup> It is claimed that the subpapillary venous plexus, not the peripheral capillary bed, is of paramount importance in regulating the depth of skin color. The dominant influence is the size or state of distention of the venules (Lewis, Wetzel and Zottermann)

to a warm fire, or after coming from a steam bath, or to that of a chronic alcoholic, or to the appearance after inhaling amyl nitrite. Frequently it has been noted from early youth, long before the appearance of symptoms. Pigmentation, usually brownish, often the result of small skin hemorrhages, is quite common in long standing cases. Nevertheless, the characteristic skin color is often absent even in cases with marked polycythemia as many authors have noted, and as Christian has particularly stressed. As the red count varies from time to time and particularly when there is a marked drop following therapy, the color change is apt to be abrupt and striking.

From time to time skin lesions supposed to be characteristic of the disease have been mentioned, but few have withstood the test of extensive study. Eczema and dryness of the skin are described. The peculiar skin lesion reported by Pick and Keznelson which was thought to be acne rosacea was much improved by the treatment of the polycythemia. This seems to be the most common skin lesion (Richter, Sequeira). A lesion recently described by Gans in a typical case of erythremia from Krehl's clinic is of interest because of its analogy to the cutaneous nodules of leucemia. It consisted of a rose red coloration over firm, irregular round or oval nodules, very tender to touch and scattered over the trunk, particularly in the lower back and abdomen. Histologically the lesion consisted of a mass of peculiar minute vascular dilatations packed with erythrocytes and surrounded by masses of cells with small round dark staining nuclei and with very little protoplasm. These cells gave the oxydase reaction. Many of the small cutaneous vessels were completely thrombosed, with marked overgrowth of the intima. A generalized purpuric eruption has been described, widespread petechial hemorrhages have been observed, and the dilatation of skin vessels over the face has been compared to the appearance in liver cirrhosis. Extensive subcutaneous hemorrhages and purpura may follow the application of poultices and heat.

The plethora and stasis of blood in all of the peripheral vessels may account for the numerous paresthesias so typical of the disease and which often present considerable similarity to the symptoms of a like nature in primary anemia. Thrombosis and phlebitis are very common and afford a possible explanation for the rather frequent association of erythromelalgia (Weintraud, Zadak, Weber, Preiss, Hollaender,



Schmilnsky, Turck, Rosengart and numerous others) At times gangrene of the foot or hand has been observed and typical Raynaud's syndrome has been described (Halir) The erythromelalgia is usually characterized by aggravation in the dependent position, when the skin color also deepens to a dark reddish cyanosis, often with edema, and with relief on elevation Cold usually affords some relief to these cases, heat makes the pain worse Often the erythromelalgia is present when no abnormality may be found on palpation of the blood vessels or x-ray examination of the affected extremity Often, however, a considerable degree of arteriosclerosis is also present The relief of pain by therapeutic measures which lower the blood count, particularly if a considerable degree of anemia is produced, is often striking There are cases, however, in which these measures do not afford much relief

The color of the mucous membranes is usually described as a deep raspberry red or like that of inflammation (Naegeli). Gaisbock thinks there is usually a marked difference in the color of the mucous surfaces depending on the presence of hard or soft underlying structures Schreyer has described the histological changes in the mucous membranes of the upper respiratory tract in two patients with polycythemia All of the smaller vessels were distended with blood, which had also extruded everywhere into the tissues As is well known, epistaxis and bleeding from the gums is common

The superficial appearance of the eyeballs is often striking A blood shot appearance may be present or there may be only a few scattered dilated venules The conjunctivae of the lids are often intensely red, suggesting inflammation The eyeground picture is well known Engorgement and tortuosity of the vessels with irregularities in width, and deep coloration of the retina and occasional papilledema are most frequently mentioned (Uhthoff, Ascher)

#### SPLENOMEGALY

The enlargement of the spleen, which was so much stressed by the earlier authors is by no means a constant finding Naegeli estimates that it occurs in about three-fourths of all cases The attempt of Gaisbock to separate out as a distinct group those cases of polycythemia without splenomegaly but with hypertension, has been rejected

by recent writers (Morawitz, Naegeli) who feel that most of Gaisbock's cases show evidences of arteriosclerosis (Eppinger), or that they represent Vaquez' Disease associated with kidney disorders (Orlowski), perhaps secondary to the hypertension of the early stages of granular kidney, or associated with essential hypertension without definite signs of kidney disease (Parkes Weber), or that they are simply examples of polycythemia secondary to arteriolar (arteriolo-kapillar) sclerosis (Münzer) Weber thinks the syndrome may represent only a phase in the course of hypertension and that the polycythemia rubra may later disappear, as in his cited case The size of the spleen varies greatly in individual patients, and at different periods in the same patient, often irrespective of treatment Both cysts and infarcts are reported at autopsy, as well as hemorrhages, perisplenitis, and the leucemic infiltrations mentioned elsewhere When treatment produces a normal blood count or secondary anemia, or even in the absence of treatment, the spleen may so diminish in size as to be no longer palpable (Weintraud, Lommel) Considerable variation in the amount of enlargement from time to time is a common clinical observation Since the majority of patients when first seen have already reached their fourth or fifth decade, it seems scarcely to be wondered at that hypertension occurs rather frequently among patients with this disease

It is usually supposed that the polycythemia antedates the enlargement of the spleen Certainly it is more frequently present than splenomegaly in the reports of those familial cases to be discussed later In Watson Wemyss' case, however, marked splenomegaly appeared before the polycythemia, and other similar instances are reported Parkes Weber considered the chief cause of the splenic enlargement to be blood engorgement, and in the light of Barcroft's recent work, this seems to be a reasonable explanation Tuberculosis of the spleen was early reported, especially in the French literature (Collet-Galle-vardin, Rennen, and others), as the primary cause of polycythemia rubra, but this theory certainly must be abandoned Winternitz mentions records of blood counts in 26 reported cases of splenic tuberculosis In six of these polycythemia was present, but in 11 an anemia was found It must be admitted however that tuberculosis, either pulmonary or generalized, has been found in many of the reported

autopsies The enlarged spleen in polycythemia rubra vera is usually quite firm and smooth and feels not unlike that of myeloid leucemia. Pain in the splenic region is very common and tenderness on palpation occurs, often more marked after treatment has been instituted The presence of a friction rub has been reported by several authors Spontaneous rupture of the enlarged and engorged spleen does not seem to have occurred in the reported cases

#### GASTRO-INTESTINAL SYMPTOMS

The symptoms referable to the gastro-intestinal tract are very prominent in a certain group of cases Either in mild or severe degree, however, they occur in the anamnesis of most patients. Loeper and Marchal have emphasized the rôle that disturbances of the blood vascular supply to the abdomen and especially abdominal plethora play in their production Feelings of fullness in the stomach, thirst, dyspepsia, gas pains and belching, and especially constipation are exceedingly common The gastric acidity is usually either quite normal or somewhat increased (Hollaender), but absence of free acid has also been reported (Watson-Wemyss, Halir and Mahler) Pain, tenderness and a feeling of tension in the left hypochondrium are of course to be attributed to the enlarged spleen Often this pain extends up into the left shoulder or down the left side and left leg More serious are the hemorrhages, often massive, which have been reported from esophageal varices, stomach and bowels The association of duodenal ulcer with polycythemia has been emphasized (Friedmann), but Bing considers this polycythemia to be secondary, and due to vomiting The frequent occurrence of hemorrhages is very important It seems most plausible to consider that these are due to the over distension of the vascular system rather than to any hemorrhagic diathesis or disturbance of blood clotting

Massive hemorrhage in this disease is one of the principal causes of death Epistaxis, bleeding from the gums, hematomata, and hemorrhage after slight injuries (as passing a stomach tube), bleeding from hemorrhoids, hemothorax (Lutenbacher), and massive hemorrhage from the lungs must be mentioned, as well as vesical, uterine and vaginal bleeding, and bleeding from the bowel, often precipitated by

diarrhoea Hemorrhage into the peritoneal cavity and into the spleen are reported (Hirshfeld), several times with fatalities Frequently extreme degrees of anemia may thus be produced in a very short time and the change in the appearance of the patient is of course most striking Regeneration of blood after such exsanguinating hemorrhages may be very rapid (one or two million cells per cubic millimeter within a week)

#### PORTAL THROMBOSIS AND LIVER INJURY

The occurrence of portal thrombosis was first brought prominently into notice by Lommel, who thought that blood stasis, often localized, was a definite if not the primary cause of polycythemia vera His thesis, which has been largely supported in the more recent paper by Kratzeisen, is that there is a certain group of cases which are secondary to long standing portal thrombosis Other cases have been reported (Emmerich) Such symptoms of occlusion may last for many years—according to Kratzeisen, in one case for twenty-six years The question remains as to whether this portal thrombosis is to be considered of primary significance, or whether it may be explained on the grounds of the well known tendency for all sorts of thromboses to occur in this disease A certain proportion of these cases appear to end in mesenteric thrombosis and gangrene of the gut, which is not so rare a finding at necropsy

Associated with this question of portal thrombosis is that of the occurrence of liver disorders in polycythemia Enlargement of the liver is of surprisingly frequent occurrence, and a note that it is readily palpable or enlarged to an abnormal extent occurs in at least one-half of the clinical reports (Brown and Giffen report enlargement in 57 per cent of the Mayo Clinic cases) Cirrhosis of the liver has been reported by Türk, Lommel, Blad, Mosse, Hess and Saxl, Schneider, Hamilton and Morse, Christian, Lowy and others) There is no doubt that it is a rather common terminal event A case of polycythemia associated with hemolytic icterus was observed for eight years by Mosse This writer considers that there is a separate group with splenomegaly and urobilin icterus At autopsy these cases are found to have cirrhosis of the liver, engorged spleen and hyperplastic bone marrow

Damage to the liver as a result of its prolonged distension with blood and disturbed circulation, and damage by reason of the excessive hemolytic activities are said to account for the production of the cirrhosis Hess and Saxl, who report fourteen cases (not all of them are quite definite), consider that with the liver disease the normal hepatic function in the destruction of hemoglobin is lost Hirschfeld considers that these cases may be primarily hemolytic icterus

Turck feels that the cirrhotic cases should be separated from those of true polycythemia vera He thinks that the quantity of the poisoning agent may determine the production of such a polycythemia A very large amount may instead lead to splenic anemia. Extensive thrombosis in the portal system seems to be very commonly present when liver injury and particularly cirrhosis is found at autopsy.

#### NERVOUS AND PSYCHIC SYMPTOMS

The nervous and psychic symptoms of the disease, together with the disturbances of the special senses are often its first and most striking manifestations Of these the most prominent are lassitude, headache, (occasionally typical migraine), vertigo and giddiness, transitory syncope, insomnia, weakness, a sensation of fullness in the head, numbness and tingling in the fingers, less often in the feet, burning sensations, and extreme sensitiveness to cold They very often bear a striking resemblance to the symptoms of mountain sickness, a fact to which Osler early drew attention<sup>5</sup> Some of the paraesthesias are curious abnormalities, as in the woman described by Parkes Weber who found that everything she touched felt wet Pruritis, usually over the extremities, sometimes generalized, is not so rarely seen, and may cause the patient very grave distress Pains in the upper legs and arms may resemble those of neuritis (E. Meyer) or of backache or lumbago Gaisbock thinks that rheumatic pains are very common, of a boring character, and may be due in part to the pressure of the swollen hyperplastic bone marrow Bottner has called attention to the increased spinal fluid pressure in many cases, as well as the relief

<sup>5</sup> "The torpor, mental and physical, the sensation of fullness in the head, with headache, vertigo and in some cases nausea and vomiting, remind us of the symptoms to which mountain climbers and aeronauts are subject"—Osler, W, *Am J Med Sci*, 1903, cxxvi, 187 Chronic cyanosis with polycythaemia and enlarged spleen A new clinical entity

which lumbar puncture affords many patients from their distressing headaches. He attributes the pressure to the overfilling of the cerebral and spinal blood vessels.

The psychic disturbances are exceedingly varied and often lead to a mistaken diagnosis of neurasthenia or of cerebral arteriosclerosis. Transient loss of memory for even the commonest events of the daily routine occur, as in the case of Freund's who forgot the way to his daily work. A college teacher that the writer once had under observation would be obliged to stop in the middle of a lecture because he had forgotten what he was talking about. Fits of emotional disturbance, somnolence, hallucinations, mental depression, and slurring of speech are not uncommon (Jung). Common visual disturbances include transitory dimness of vision, or even temporary blindness, scotomata, specks and bright points in front of the field of vision, diplopia and temporary paralysis of one of the extrinsic eye muscles. Ringing and roaring in the ears is exceedingly common. Meniere's syndrome has been reported several times. Schreyer attributes its occurrence to the distention and congestion of the vessels of the middle ear. In the apoplectic form cases he states that there is bleeding into the labyrinth. The most serious complications of the disease, cerebral vascular lesions, frequently hemiplegias, are usually considered to be due to thrombosis because of the slowness of development of the paralysis and of the findings at autopsy. Cerebral hemorrhage however plays a most important rôle. Zadak reports a case in which a fatal cerebral bleeding was the first known symptom of the disease, and another similar case has recently been observed by the writer. Umney's case of chorea which appeared prior to extensive thromboses over the entire body is very interesting. Other cases of chorea, reported by Bordachvi and by Pollack, seem to have been due to organic cerebral changes, hemorrhage or thrombosis. Both spontaneously improved, apparently without any direct relation to changes in the blood count.

Christian has drawn attention to the interesting superficial parallel between the sensory symptoms of polycythemia and those of pernicious anemia. So far as we are aware, anatomical evidences of similar cord changes have not been found at autopsy in polycythemia. Many writers lay stress on the rôle of polycythemia in many obscure neuro-

logical diagnostic problems To mention only a few, it has been held responsible for the symptoms of cortical military hemorrhages, multiple arterial or venous thromboses, false tumors with choked disks, muscular twitchings of obscure origin, epileptiform attacks, and all sorts of attacks of temporary loss of consciousness with or without paralysis

#### BLOOD AND BLOOD FORMING ORGANS

Of the two pathological changes regularly seen in polycythemia vera, that of primary etiological importance seems to be the extensive hyperplasia and proliferation of the red bone marrow Detailed descriptions of the gross and microscopic appearance of the bone marrow have been made from material removed during life (Watson Wemyss) as well as from that obtained at autopsy Zadak considers that bone marrow puncture *in vivo* (sternum) is of considerable diagnostic importance in doubtful cases Enormous numbers of mature erythrocytes as well as normoblasts are present Megaloblasts are rare. The white cells are also enormously increased in numbers with many myelocytes. Neutrophilic leucocytes are said to be proportionately diminished, eosinophils are prominent The magakaryocytes are often increased No essential differences in the picture in autopsy material are reported Hirshfeld's description is typical. There was widespread conversion of the fatty marrow into red marrow in all of the bones and the blood spaces were crowded with erythrocytes He found all varieties of leucocytes also present and concluded that so far as the proportion of this type of cell was concerned, the hyperplastic marrow did not differ much from normal red marrow. The stimulus to proliferation appeared to affect all the elements to about the same degree. Differential counts of bone marrow material made according to the technique elaborated by Sabin and her pupils would be of the very greatest interest and importance It may be asked why the mature polynuclear cells as well as their unripe forms do not commonly appear in corresponding numbers in the circulating blood As will be indicated later, a certain increase in these elements does indeed seem to occur very frequently. The situation presents some slight analogy to that of primary anemia where an increased new leucocyte formation does occur along with the increased erythropoiesis, but it is not regularly reflected in the circulating blood It seems very

likely that the physical conditions governing the discharge of the new erythrocyte elements from their site of origin in the marrow differ from those regulating the discharge of the new white cell forms (Sabin)

The enormous increase in the concentration of erythrocytes per unit of volume, as well as the tremendous increase in the total blood volume throughout all of the tissues of the body seems to be a direct consequence of the bone marrow hyperplasia. The blood count in polycythemia vera may vary from a comparatively slight increase above the normal up to thirteen or fourteen millions. The case reported by Jedwabnik, (with twenty millions), (Inaug Diss, Berlin, 1913, mentioned by Hirshfeld) seems almost incredible. The count varies appreciably from day to day. Hirshfeld, as well as Gaisbock, considers that simultaneous determinations of the blood count from venous and arterial blood show in general no marked differences. Such is also the conclusion of the writer, both from erythrocyte counts and from estimations of the oxygen capacity, both in polycythemia vera and in the polycythemias of chronic cardiac and pulmonary disease. Differences occur, but they are in general neither constant nor characteristic. Fitz believes the red cell count in the secondary polycythemias is lower in the arterial blood.

No characteristic qualitative differences have been found in the properties of the hemoglobin of polycythemic blood. Thus Butterfield found normal relations to exist between iron content, gas binding properties, and spectrophotometric behavior. A recent study by Bauer, Lawronsky and Skujin claims to show that with increased hemoglobin content of blood there exists, in general, a lessened oxygen saturation.

Of the physical properties of the blood, the increased viscosity probably stands first in physiological significance. It is stated that it may be five to eight times greater than in normal blood. It is primarily due to the great excess of red blood cells over plasma. The viscosity of the serum, indeed, is said to be less than normally found in health (Lommel). The size and shape of the erythrocytes in general and the cell diameter is said to be normal (Gutzeit and Lommel). The writer has found no difference in the respiratory metabolism of the erythrocytes or in their glycolytic behavior as compared with normal human blood (unpublished results). Anisocytosis



sis, microcytosis and polychromasia, as well as normoblastosis and less frequently megaloblastosis, however, are often found (Hurder, Senator, Lommel, Tancre, and many others) Very large increases in the reticulocytes (unless after severe hemorrhages) are unusual The fact that immature cells and reticulocytes are usually present in comparatively small numbers in polycythemia vera may be an indication that a balance has been reached between the hyperplastic marrow and the circulating blood, just as occurs in the reaction to high altitudes, as Drinker pointed out in commenting on Forbes' results at Cerro de Pasco During the process of acclimitization increased reticulocyte counts were found, but in natives, whose cell count might be eight million or more, no noteworthy increases over the normal reticulocyte concentrations were noted An increase in the erythrocyte count relative to the hemoglobin is practically a constant finding in polycythemia vera, so that the color index is always less than 1 It is generally conceded that a considerable leucocytosis is very common and the differential count often shows an increased percentage of polymorphonuclear cells (75 to 85 per cent or even higher) Many cases have counts between 15,000 and 25,000, and not a few cases are on record in which a leucocytosis of from 25,000 to 40,000 is reported The blood platelets are normal in number or they may be somewhat increased (Turck Zadak) According to Ludin and Herrnheiser the fibrinogen content of the plasma is diminished Naegeli cites several authors to the effect that the serum albumin is reduced One of our cases, before treatment, showed normal values for the serum proteins

Regarding a number of constituents of the blood the reported analyses are so conflicting as to give the impression that no characteristic or markedly abnormal finding probably occurs These include the concentration of cholesterol, total serum proteins (said to be diminished by Senator), the serum globulin-albumin ratio, the blood fats, serum bilirubin, the concentrations of the various inorganic anions and cations in the serum,<sup>6</sup> and the various non-protein nitrogen constituents

<sup>6</sup> In a paper read at the meeting of the American Society for Clinical Investigation (May 1928), Brown reported an increase in the serum calcium in cases of polycythemia vera, which diminished with phenylhydrazine treatment He believes this to be of significance in relation to the known tendency to vascular thrombosis

The evidence concerning the time of blood clotting in polycythemia vera is somewhat conflicting. The majority of publications state that the blood clots with abnormal rapidity. This abnormal tendency to clotting, together with the slowing of the blood flow and temporary stasis in many areas then furnishes an explanation of the frequency of thrombus formation. But against this assumption is the frequent occurrence of hemorrhages. It is not impossible that variability in the tendency to blood clotting may occur with different phases of the disease in the same patient. Slow retraction of the clot and slow clotting *in vitro* have been observed by several writers. The bleeding time is variously stated to be normal or somewhat delayed.

The volume of blood in erythremia as measured by both the dye and carbon monoxide methods appears to be greatly augmented, a fact which is in close agreement with clinical observation and the findings at autopsy. Among others, it has been noted by Haldane and Boycott, Morawitz and Siebeck, von Bergman and Plesch, Bock, Lampe, Seyderhelm, and Brown and Giffen. Most authors consider the increase due to an increased volume of the red cells, the volume of the plasma remaining unchanged. Beltz and Kaufmann, however, have reported a diminution in the plasma volume. The increased density of the x-ray shadow of the bronchial vessels has also been evidenced by Rover in support of an increased blood volume. The blood volume may be increased according to some of these reports to twice or even three times the normal value. Berger, using the trypan red method, has recently reported a case with a blood volume of over ten liters, or about 17.6 per cent of the body weight. There is not only an enormous increase in blood in the organs in general but the smaller vessels of the pia mater of the brain and cord are engorged and distended with blood.

Studies of the skin capillaries by direct observation have been made by Brown and Giffen (1923, 1926). They report a distention and enlargement of part or of all of the capillary loops, particularly of the venous segments, and the opening up of all available vessels. The blood flow was much retarded. The observations of Koenigsfeld (mentioned by Engelking), as well as those of Hisinger-Jagerskiöld confirm these findings. The remarkable ability of veins and capillaries to store an enormously increased blood volume under experimental conditions has been pointed out by Meek and Eyster. They found

that 30 or even 100 per cent of the original volume may be added to the circulation without producing cardiac dilatation. Brown and Giffen point out that additional vascular space is made in the skin vessels at the expense of a loss or impairment of the physiological heat mechanism. They attribute to this many of the sensory symptoms such as intolerance to heat and cold, and the burning sensations of which many patients complain.

Because of the accumulated evidence that the spleen plays a rôle in blood destruction, it has been assumed that its enlargement in polycythemia vera may be associated with an increased amount of blood destruction. The diminution in the size of the spleen which often occurs after the lowering of the erythrocyte count and hemoglobin during treatment with phenyl hydrazine and radiation has already been mentioned. This may be preceded by a temporary increase in size during the period of increased blood destruction. The whole matter is bound up not only with the very obscure rôle of the spleen in blood destruction but probably also with its other and better understood function as a storehouse for red blood cells.

Marked variations are said to occur in the fragility of the cells in saline solution. Minot and Buckman observed an increased resistance range, an increased hemolysis (fragility), complete hemolysis at a NaCl concentration definitely below the lower normal limit, and a "trickling effect." These authors also discuss the response of the cells to serum dilutions. They conclude that such behavior indicates an active hyperplastic marrow, with cells of many ages, particularly immature cells, in the circulation.

An increased output of urobilin has been observed at times during the course of the disease (Minot and Buckman) and a slight excess of bile pigments is occasionally observed. These are, however, by no means constant findings. Naegeli, for example, states that no increase occurs in the urobilin output. Halr and Mahler in a recent article think it is reduced. The large and inconclusive literature on this question is reviewed in the various monographs. Increased amounts of bilirubin in the blood (van den Burgh reaction) have been reported in a number of cases (Zadak). We have found no significant increase in our untreated cases. As regards the general question of blood destruction in polycythemia vera, one must conclude that

although in some instances, and perhaps from time to time in every patient, there may be indications of a temporary increase, this phenomenon has not been demonstrated to be either a regular or a characteristic accompaniment of the untreated disease. All of the present day evidence goes to show that alterations in blood destruction can have but slight direct influence upon the polycythemia.

#### POLYCYTHEMIA RUBRA AND MYELOID LEUCEMIA

A considerable number of typical cases of polycythemia rubra have now been reported in which anemia of greater or less severity has developed during the course of the disease and the clinical picture and the appearance of the blood has come to resemble that of myeloid leukemia. When death has occurred the appearance at autopsy has often borne out this clinical likeness. Blumenthal's frequently-cited case with a leucocyte count of 16,300 had 36 per cent of neutrophilic myelocytes, 9 per cent were "mast cells," and the erythrocyte count was 11.4 millions. Numerous other observations have been reported, among which may be mentioned those of Brieger and Forschbach (who give a brief review of the literature on the occurrence of marked leucocytosis in erythremia), von Winterfeld, Pendergrass, Hedenius, Rosin, Erich Meyer, Hirschfeld, Zypkin, Jung, Daniels and v Buchem, and finally the important study of Minot and Buckman. These latter authors consider polycythemia to be comparable to chronic myelogenous leukemia and believe that there is much evidence that both are neoplasms of the hemopoietic tissue. They believe that abnormal forms are almost constantly present among the red cells in the circulating blood in erythremia, and in most instances immature cells may be found. The abnormalities in the blood picture consist in unevenness of depth of staining, occasional polychromatophilia, often achromia, and at times the occurrence of macrocytes, microcytes, and erythroblasts.

Reticulated cells, they find, may actually be decreased in numbers as also may occur at the height of a remission in primary anemia, while an increased white cell count is almost constantly found and a few, occasionally many, immature white cells may be present in the circulation. They draw attention to the fact that the platelet elements may also become involved, as in myeloid leukemia, the number may in-

crease in the blood stream and megacaryocyte nuclei may enter the circulation. Three of Minot's cases out of the fifteen reported developed an anemia which suggested primary anemia in the peripheral erythrocyte picture, while the white cell picture was compatible with that of myelogenous leucemia. Autopsy in one case revealed a spleen weighing 3200 grams which showed remarkable myeloid transformation, and the liver also appeared leucemic. In Brieger and Forschbach's case, an acute myeloblastic leucemia followed a period of x-ray therapy, but after an interval of four months. Curious leucemia-like blood pictures have been observed by Rencki and by Schneider after splenectomy, and by Hirshfeld after radiation of the spleen. On the other hand, true polycythemia is reported after splenectomy necessitated by traumatic rupture of the organ.

Polycythemia has also been reported as developing in cases of typical leucemia, the reverse sequence of events, notably by Ghiron and by Winter. The former observed during the course of typical myeloid leucemia an increase in the erythrocyte count to 7.2 millions and at the same time a marked erythema of the face. Turck believes myelocytes are very commonly present in the circulating blood, as do many writers, and he emphasizes his belief that the disease is completely analogous to myeloid leucemia. Naegeli states that myelocytes are frequently to be found in the circulating blood and that eosinophils are often increased in absolute numbers. Nevertheless he rejects the theory that a combination of leucemia and of polycythemia occurs. All of these cases he considers to be myeloses with an initial high erythrocyte count. The termination of polycythemia in the clinical picture of pernicious or of aplastic anemia, but without the typical high color index, is noted also by Freund and by Hirschfeld. A case of so-called "total leucemia" is described by de Guglielmo, in which erythrocytes (7.5 millions), leucocytes and platelets were all increased and their immature forms all present in the circulating blood. In Parrisius' case, the blood picture seemed to show the simultaneous occurrence of polycythemia and leucemia. Cases of typical polycythemia with relatives suffering from leucemia are reported by Gutzeit (case I) and by Guggenheimer. The latter's patient was a young woman of twenty-nine. Her symptoms of polycythemia dated from the time when she acted as blood donor for her mother, who had

leucemia The effect of too severe or too prolonged x-ray treatment is reported by Detre, in whose patient after radiation at intervals during two years the erythrocytes fell to 720,000, with almost no platelets and only 3000 white cells Schmidt reports a similar case where the initial erythrocyte count was 13,800,000 After a series of deep x-ray treatments, death occurred, from an intercurrent infection, and autopsy showed the bone marrow almost entirely fatty All of such cases seem to be the results of excessive radiation and not peculiar to polycythemia

The question arises as to the true explanation of the anemia, and the aplasia which seems to have been the terminal event in many cases The most plausible hypothesis is that after many years of excessive erythroblastic stimulation and hyperfunction in this chronic affection, the blood forming mechanism at last gives away under the strain and a disorderly proliferation of all types of leucoblastic elements occurs just as in leucemia The intensive treatment which many patients now receive, whether radiation, benzol, repeated venesection, or phenyl hydrazine, no doubt may be responsible at least in part for these findings and for the bone marrow aplasia in some of the reported cases

The striking thing, in the opinion of the writer, is that even the most carefully reported studies only serve to demonstrate the exceptional occurrence of blood cell abnormalities in the disease as a whole and the fact that from both a physiological and morphological point of view the cells are in the main quite normal On the other hand, the disease polycythemia rubra when viewed strictly from its clinical aspects bears little analogy to leucemia Indeed, if it must be compared to another blood disease both in symptoms and in clinical course, that disease is primary anemia It is essentially a long standing chronic malady There is little question that in the majority of cases it is present over a very long period of years before its presence is discovered or the patient comes to the physician for relief Far from running the ordinary progressive course of leucemia, it tends to remissions over long periods If the patient escapes becoming a victim to the more serious complications—the tendency to hemorrhage and thrombosis, and the increased sensitiveness to intercurrent infections—the disease appears to have an indefinite course A number of cases essentially unchanged have been observed for periods of ten to fifteen years

## PHYSIOLOGICAL STUDIES IN POLYCYTHEMIA VERA

A moderately increased basal metabolism in the majority of patients with polycythemia vera, which does not seem to be directly related to the degree of erythrocyte or hemoglobin increase in the peripheral blood has been reported by many authors. Abbott, Isaacs, Minot and Buckman, Brown and Giffin, and others have recently reported observations not mentioned in earlier reviews. To these cases the author can add the observation of an increased metabolic rate in fifteen cases at the Johns Hopkins Hospital, ranging between +4 and +52. A reduction in the basal metabolic rate may follow reduction in the degree of polycythemia by means of therapeutic measures (phenyl hydrazine, radiation), but this is not invariable. Polycythemia complicated by hyperthyroidism has been reported by Tyrrell, but insufficient data are published to give one confidence as to the diagnosis in this case. Zadak's well studied case, however, is of great interest. Obviously it is a rare complication. In this connection it may be proper to state that there are many suggestions in the literature, but no evidence, that polycythemia may be a purely endocrine disorder. It has been described in association with proven Addison's disease (Romberg), tetany, and eunuchoid obesity, as well as hyperthyroidism. There is indeed some evidence that the thyroid gland may be concerned in some way with the regulation of erythropoiesis. Mansfeld claims to have produced polycythemia (up to eight million cells) in dogs and rabbits by the injection of thyroid juice. The association of anemia with myxoedema is well known.

A diminished circulatory minute volume (recumbent position, fasting) has been reported by Liljestrand (see also von Bergmann and Plesch). It has also been observed by the writer (unpublished experiments). The slowed blood flow was accelerated by the reduction of the blood cell volume produced by radiation and phenyl hydrazine treatment.

In polycythemia, as was clearly shown by Lundsgaard, there is a lowered coefficient of oxygen utilization. This is of especial interest in view of the lessened blood flow, which in blood of normal oxygen carrying capacity would be expected to produce a change in the opposite direction. The oxygen saturation of the arterial blood is usually normal, or at least at the lower limits of normal. In three cases,

however, Harrop and Heath found a significantly increased arterial oxygen unsaturation after exercise. They attribute this to changes in the rate of pulmonary gas diffusion. The surface temperature is often low a consequence, according to Senator, of the slowed blood flow.

The respiratory symptoms in this disease are rather conspicuous although they are not stressed by many writers. Dyspnea on much exertion is the rule in most cases of outspoken polycythemia, and it is a common thing to find an increased respiratory minute volume (Senator, Schill, Isaacs). The vital capacity of the lungs is often very considerably reduced, a condition which has been attributed to the intense pulmonary vascular congestion. Many of these patients acquire respiratory infections very easily and the frequency of chronic bronchitis as well as moderate emphysema is remarked by a number of authors. Gutzzeit mentions cases with onset following pulmonary disease. Very prominent lung markings are noted in x-ray pictures of the chest by Römer. This writer is not very clear as to whether these are due to increased bronchial markings or to the general vascular congestion. I have studied a series of chest x-ray photographs of cases before and after therapeutic measures have been carried out which have greatly reduced the erythrocyte count and the blood volume. It seems clear that the increased x-ray density may be due to both causes. The bronchial markings remain, while the diffusely increased density of the x-ray shadow may be lessened when the blood volume is reduced.

A diminution in the rate at which gases (oxygen and carbon monoxide) pass through the pulmonary epithelium has recently been demonstrated by Harrop and Heath (by means of the Krogh method for determining the pulmonary gas diffusion constant) in seven cases of polycythemia vera. These authors suggest that in these cases there is an actual reduction in the arterial  $\text{pO}_2$  or oxygen tension, not to be observed from the arterial oxygen content, and that this may constitute the stimulus to the increased erythropoietic activity. Whether this stimulus is directly upon the bone marrow tissues or whether it is indirect as by means of an alteration in hormonal control from some center which is especially sensitive to the stimulus of anoxemia, it is not possible to say. The striking similarity existing between the symptoms of mountain sickness and those of polycythemia vera



was long ago shown by Osler, and it is noteworthy that the pulmonary gas diffusion constant is also diminished in persons who suffer from mountain sickness, to an extent which is approximately proportional to the severity of their symptoms <sup>7</sup>

An improvement following the use of oxygen inhalations in patients with polycythemia vera has been claimed by v. Koranyi and Bence. The red blood cell count was reduced and the blood viscosity lowered. Other authors have been unable to confirm this observation, and this method of treatment has been generally disregarded, although Gutzeit has found it of value in conjunction with x-ray. The writer has found no change whatever in blood count or oxygen capacity following the inhalation of pure oxygen for a period of three hours in a case of polycythemia, and Binger was unable to produce significant changes after several days' residence in an oxygen chamber (40 per cent oxygen) at normal barometric pressure <sup>8</sup>. Parkes Weber mentions an unpublished case of E. P. Poulton's in which residence in an oxygen chamber had no marked effect. Winter also tried the effect of placing his patient in a compressed air chamber without effecting any change in the erythrocyte count.

Nearly all writers are agreed that splenectomy in this disease is absolutely contraindicated. Brieger and Forschbach observed a

<sup>7</sup> Professor Carlos Monge of the Facultad de Medicina, Lima, Peru, has informed me (personal communication), that during the course of an expedition last year to Oroya and Morococha, in the high Andes, he found a large number of cases of true polycythemia with characteristic physical signs and symptoms. He has demonstrated the existence of cases of prolonged soroche (mountain sickness), as well as mild cases of more or less "benign" erythremia, which he considers to be an intermediary stage between soroche and severe typical erythremia. These intermediate cases were found among all groups studied—comparative newcomers, residents of several years, and even among the natives. This important study for the first time indicates that true typical polycythemia may be produced as a result and direct sequence of mountain sickness, and may be caused by the same stimulus, low oxygen tension. It is the outcome of an earlier investigation transmitted to the Academia de Medicina de Lima in 1923. In this communication he reported a severe case of polycythemia vera apparently due to life at high altitudes, and suggested the possibility of the prevalence of the disease in those regions.

Sir Humphrey Rolleston has kindly drawn my attention to the case reported recently by Barnes Thomson and Lamb in which a diffuse infiltration of the pulmonary alveolar walls by tumor tissue took place, undoubtedly impeding gas diffusion to an extreme degree and producing a marked polycythemia.

<sup>8</sup> Personal communication.

severe case of erythremia for thirteen years, the onset of which definitely followed the removal of a spleen necessitated by traumatic rupture. The case reported by Sauer is very striking. In this case death followed splenectomy after the erythrocyte count has risen from six and one-half million to twelve million cells. At section evidences of portal thrombosis were found. Kratzeisen's case is somewhat similar. The spleen, removed at operation, showed multiple infarction and thrombosis of the splenic vein. Death occurred six months after operation and portal and mesenteric thromboses were found at autopsy with intestinal gangrene. Comminotti, Renchi, and Blad also report fatalities. The development of leucemic-like conditions has been mentioned above, as a sequel to removal of the spleen.

The use of venesection is practically always attended by immediate subjective improvement. According to Horder small venesections are insufficient, at least 500 cc must be removed. The loss of blood at parturition has had a favorable influence (Paulicek). Unfortunately in a large number of cases venesection appears to act as a further stimulant to the bone marrow and return to the original erythrocyte level in the peripheral blood may be very rapid. The author has observed the blood count in a case after a large bowel hemorrhage rise from 3.5 million to 6.8 million in the course of a week. Guggenheimer's patient, who commenced to have symptoms of polycythemia vera shortly after giving a large amount of blood for a transfusion has already been mentioned.

Drinker points out that there are two ways of producing "normal" marrow proliferation by blood loss and by means of low oxygen tension. He states that if animals are bled small amounts repeatedly, although normoblasts are to be found occasionally in the blood it is possible by keeping the blood withdrawal low to induce a high degree of marrow hyperplasia without the appearance of any considerable number of nucleated red cells in the circulating blood. This is analogous to the usual state of affairs in polycythemia. On the other hand, if the hemorrhages are large, both normoblasts and megaloblasts may be found in the blood stream. One must conclude that while venesection is an important and useful relief in emergency in the treatment of these patients, it cannot be looked upon in any other light than as a further, and therefore undesirable stimulant to new blood formation.

The frequent appearance of polycythemia following an infectious

disease is stressed by Gutzeit, who feels that such an event in some way destroys the balance regulating erythrocyte production. One can recall the interesting sequence of events in Freund's case where splenectomy and pneumonia were both complicating factors. The rôle of infection is also emphasized by Weintraud and by Gaisbock. Benda finds a parallel increase of erythrocyte count and cholesterol concentration in gravid women. Many authors are impressed with the lower resistance of these patients to all sorts of infections.

The question of how frequently cardiac hypertrophy, or a mild grade of cardiac insufficiency occurs is not settled. Certain writers lay great stress on the usual absence of cardiac changes in the uncomplicated disease, but both are nevertheless frequently reported. In eight cases studied by Hollander the size of the heart as measured from the x-ray shadow was quite normal even with increased blood pressure. The series reported from the Mayo Clinic (Brown and Giffin), and many others emphasize the frequent absence of cardiac enlargement. Del Baere considers that it takes less blood to supply the tissues with sufficient oxygen, hence there is less cardiac work in spite of increased viscosity or even hypertension in polycythemia. On this line of argument, Parkes Weber considers polycythemia a favorable sign in persons with high blood pressure. It seems quite clear that the extraordinary increases in blood volume which these patients show may occur with a cardiac mechanism which shows no anatomical changes over long periods and no appreciable physiological strain. On the other hand, hypertension, if present before treatment, may persist even when the blood volume is greatly reduced, although some relief is not unusual. Some writers however lay stress on the occurrence of cardiac symptoms late in the disease, the heart eventually giving away, although for years no injurious effect had been previously felt. For instance Bottner, in a recent article recognizes three stages (1) an early stage only detected from the blood picture, (2) an intermediate stage with outspoken symptoms of typical character, and (3) an end stage with venous stasis and cardiac decompensation. Some writers would discard as cases of secondary polycythemia all of those with cardiac symptoms. This seems to be an unwarranted standpoint. Final death from cardiac failure is common in patients who escape the fatal effect of massive hemorrhages or other vascular accidents.

## POLYCYTHEMIA AS A CONSTITUTIONAL OR FAMILIAL DISEASE

An important recent development in the study of the etiology of polycythemia vera is the evidence which is accumulating of its occurrence as a constitutional or familial disease. Curshmann claims to have been the first to stress this constitutional factor. He describes three families in which several persons suffered from the disease and argues that many members of such families may never have the severe progressive disease of Vaquez, but only possess a high color and symptoms not severe enough to require medical assistance. They go through life with such an "erythremic constitution" and in old age may die of intercurrent infections. Engelking describes a remarkable family in which five children (two brothers and three sisters) as well as the mother and grandmother, certainly seem to have had typical symptoms of polycythemia vera with outspoken blood changes. The members of this group considered that "verfrorenes blut" was a family characteristic. In several members the spleen was much enlarged and a rather well marked infantile habitus was noted. Engelking regards the eyeground changes as typical and quite distinguishable from those of the polycythemia of congenital heart disease, although this opinion is not shared by others. He thinks the cause of the disease is probably a lack of balance in the hormonal control of the hematopoietic system, a conjecture which Naegeli also considers possible. Hedenius regards it as essentially due to a constitutional insufficiency of the endocrine balance. Wieland publishes an account of a family in which the disease apparently occurred in three generations. He had an opportunity to study the mother and five living children, four of whom had definite evidences of the disease. None had hypertension, or a palpable liver or spleen. Signorelli reports the occurrence of polycythemia in two sisters. Herz describes the disease as an inherited affection in thirteen cases belonging to four different family groups under his observation. Another family with three affected children is described by Kretschmer. Stoye's case in a three year old child was associated with constitutional obesity and gigantism. Doll and Rotschild report polycythemia in two sisters of a family, four of whose members had Huntington's chorea. The probability of its occurrence in the mother as well as the brother of Owen's patient may be recalled, although the evidence presented was not quite con-

clusive. Gutzeit's case (no 4), a youth of nineteen had a mother and two sisters with evidences of the disease, although none had ever consulted a physician. Tancre's remarkable case with the erythrocyte count of 14 2 million, 178 per cent hemoglobin and 18,300 leucocytes had a sister with a red cell count of 6 1 million, but no symptoms. Nichamin's patient, a girl of twenty, had been known to have a palpable spleen since early childhood, and had a sister in which the same finding was noted. The mother as well as the patient and her sister had deep red skin color. Zadak mentions a family in which two sisters were affected.

The slow insidious onset of the symptoms of this malady and the fact that it is preeminently a disease (or, better stated, it becomes a disease) of middle and late middle life, constitute two of its most striking features. It is certain that the polycythemia and the splenomegaly, as well as the characteristic skin color have existed for years in many patients before their symptoms finally send them to a physician. Moewes' case, a young man of twenty-three (whose mother also apparently suffered from the disease) and who appeared for relief on purely cosmetic grounds, having noticed the dark red color of his face for a period of three years, furnishes a good illustration of this point. When first seen this patient was entirely devoid of any other subjective symptoms, although he was obviously suffering from typical and full blown polycythemia vera. This case, which is reported with detailed pathological findings, is an example of the termination of erythremia in chronic nephritis (parenchymatous) with uremia, although the question of the relation of benzol therapy to the outcome is an open one in this particular case.

The termination in chronic nephritis is not uncommon, particularly in the group with hypertension and arteriosclerosis. Curshmann and Gaisbock mention the frequent occurrence of chronic kidney disease, while Munzer, and Dietl and Fritz, suggest that arteriosclerosis is actually a cause of polycythemia vera. Turck and Rosengart believe that the albuminuria which is so commonly found is due to blood stasis in the kidneys. The interesting association with orthostatic albuminuria has been described by Weber, and by Herrnheiser. The associated paroxysmal hemoglobinuria reported by Pel would seem most likely a phenomenon secondary to the polycythemia itself.

## TREATMENT OF POLYCYTHEMIA

A very large number of therapeutic measures have been employed in the treatment of polycythemia vera, most of which have proven to be useless. The use of oxygen therapy and of venesection has been mentioned above, as well as the contraindication to splenectomy. Employment of an iron free diet, suggested by Ehrlich, has had no effect. It is a mistake, with our present knowledge, to make these patients unhappy with ill considered dietary restrictions. The use of agents to produce blood destruction (and apparently a depression of bone marrow activity) has been chiefly limited to the employment of benzol, introduced by Koranyi, and of phenyl hydrazine, which was introduced by Eppinger and Kloss in 1918. Although a number of enthusiastic reports appeared some years ago on the use of benzol, its employment has now fallen into disuse. The effect of the drug on the white cells, the difficulties met with in regulating its dosage, and the extremely serious and distressing results of benzol poisoning have combined to cause its abandonment at the present time in favor of phenyl hydrazine.

A number of papers have appeared reporting clinical experiences with the latter drug. Those enthusiastic for its use have reported no evidences of liver injury, although the occurrence of jaundice is not very uncommon in the course of treatment. The drug is usually given in courses, varying from one gram to six or eight grams over a period of several days. Evidences of blood destruction commence early, an increase of serum bilirubin (indirect Van den Bergh) often being noted after the second dose (0.2 gram). The effect continues to be observed for seven to ten days after it is discontinued, a drop of as much as a million or more erythrocytes often still taking place. Owen noted the occurrence of leucocytosis early in the treatment and suggested that this leucocytosis might serve as an index of the amount of the drug required. This in general seems to have been borne out in our subsequent cases. There is an increase in the reticulocyte count. The change in the blood platelets has not been very striking. The serum bilirubin curve seems to bear some relation to the blood destruction. Long has pointed out the appearance of methemoglobinemia. Slight icterus during treatment seems to have been

common in the cases studied at the Mayo Clinic. The increased blood volume characteristic of the disease is said to diminish during the treatment coincident with the erythrocyte destruction and is manifested in a diminution in the cell volume (Brown and Giffin). These observers found no evidence of hepatic damage with therapeutic doses. Levi however thinks that phenyl hydrazine increases the damage to the liver if injury is already present. The symptoms observed during the course of treatment are usually mild but may include gastrointestinal disturbances and particularly nausea and vomiting. Anorexia is the rule as well as general weakness during the period of rapid blood destruction. There is often well marked tenderness over the spleen which may become still more enlarged during the earliest stage of treatment. Hematuria and slight hematemesis have been reported (splenic and renal infarcts?). The appearance of very dark urine, especially on standing, is well known. The urine usually contains a reducing body. Infarctions of the basilic vein and of a superficial leg vein have also been noted. Since thrombosis is common in untreated polycythemia one cannot be certain that phenyl hydrazine was responsible in these instances.

The relief afforded from a reduction in the erythrocytosis, and as it seems, from a reduction in the blood volume produced by any of the therapeutic procedures which have been employed is usually very striking and affords evidence of the fact that most of the symptoms of this disease are directly referable to the disturbed circulatory mechanism. The vertigo, fullness in the head, headaches, neuritis, eye symptoms, tinnitus, weakness and mental symptoms, are usually greatly relieved when sufficient doses are given to lower the count to normal or even to produce some secondary anemia. Pain in the muscles, bones and joints is usually markedly lessened. This is especially noticeable in those cases of pain in the legs with calcification of the arteries. It is an interesting fact that the reduction in the blood volume does not always reduce hypertension, if it has existed. This may be correlated with the common observation that there is usually little or no cardiac hypertrophy visible in cases of polycythemia without hypertension.

A decided elevation of the blood urea and non protein nitrogen and a slight elevation in the creatinine have been reported during phenyl

hydrazine treatment, apparently correlated with the degree of cellular destruction. There were no changes in the blood uric acid. The amino acid nitrogen, which is said to be increased in the blood in polycythemia, falls to normal with treatment. The tests for liver function showed no evidence of liver impairment in Huffman's cases with phenyl hydrazine therapy. Evidences of temporary renal insufficiency were noted in one case (functional tests). No alterations in the basal metabolism followed treatment in his series.

The acquirement of "tolerance" to the drug upon repeated injection has been noted in animals and it is also present in patients (Taschenberg). One of the author's cases in which a reduction of the erythrocyte count from 9.5 million to normal was at first produced with one course of 2.0 grams has subsequently failed entirely to respond after a course totalling 9.5 grams. Altnow and Carey report the presence of fairly large numbers of nucleated red blood cells and 8.4 per cent of reticulocytes on the twelfth and thirteenth day of phenyl hydrazine treatment. A case reported by Long had 46 per cent of reticulocytes and the red cells sank to 1.5 million necessitating transfusion. Long has produced an increase in reticulocytes up to 60 per cent in rabbits with this drug.

The use of radiation (both roentgen ray and radium) in the treatment of polycythemia has been the subject of many articles, only a few of which may be mentioned here. The opinions of the writers betray all shades of enthusiasm, from the report of Schoning who treated three cases in Lommel's clinic with the result that they were "clinically cured," to those who attribute the death of their patients to the effects of  $\gamma$  ray. The long bones have been the favorite site of  $\gamma$ -ray treatment, together with sternum and ribs. Naegeli considers radiation of the spleen useless, and Hirshfeld has reported the onset of myeloid leucemia as a consequence. It is supposed to be theoretically contraindicated for the same reason as splenectomy because removal of its physiological effect should act as a bone marrow stimulant. Brieger and Forschbach's case may also have been due to the use of  $\gamma$  ray. On the other hand, Burnam has recently had cases, three of which have been observed by the writer, where the blood count has been lowered and great clinical improvement has apparently been produced by the use of radiation over the spleen. The first effect



in the cases which I have observed has been an increase in the size of the spleen and an increased erythrocyte count. The radiation was combined with phenyl hydrazine treatments. An excellent result is reported by Rydgaard which followed x-ray of the spleen. At the time of his report the effect had lasted eighteen months. Gutzeit, who advocates the use of deep x-ray, believes the dosage is subject to great individual variation and must be carefully regulated and controlled by frequent blood examination, an opinion which everyone will certainly endorse. Like most recent observers, he believes results are only to be expected of treatment over the bones, with careful control by frequent study of the blood picture. He believes polycythemia vera is due to a disturbance of the organ system or hormonal control which regulates erythropoiesis. Hence therapy can only be symptomatic in its effect. Good results from carefully regulated doses of radium over the bones are reported in Hogler's recent article from Falta's clinic. This author believes that radium works more intensively than x-ray. It is possible that it may produce a more extensive scarring, which seems to be the principal effect of both forms of radiation. A well studied case is reported by Leudin with gratifying results from long continued x-ray of the bones. The author considers one might almost speak of cure were it not for the reappearance of myelocytes in the blood. Bottner thinks "irritative," or "stimulative" radiation to the spleen may be used as well as radiation of the bones, in order to stimulate its hemolytic action. Schultze found such great improvement in one case after radiation chiefly over the bones that he considered the patient "clinically cured." He reports the occurrence of jaundice after radiation of the spleen and long bones. Mosenthal considers radiation over the spleen reduces its size but produces very little effect on the blood picture. On the contrary, he finds that radiation over the bone marrow produces a lasting improvement. He used frequent small doses gradually increasing in amount, and the symptoms remained completely absent for two years. Of Steiger's four cases, the one radiated over the spleen was improved clinically with the subsidence of the enlarged spleen but the blood count was not changed. Marked changes in the blood count occurred in the other three, who received bone radiation. Rosenfeld has reported a favorable experience with Thorium X. The interesting re-

sults which Head reports from radiation over the spleen combined with benzol in a case which he considers as tuberculosis of the spleen seem to the writer to be on the contrary an example of the prolonged chronic course of polycythemia vera, with typical remissions and with the usual lack of lasting effects from this type of treatment

On the whole, the experience to date seems to be against spleen radiation and in favor of small doses in a prolonged course over the long bones. Thus Luedin's case received ninety-four doses and Forschbach's ninety doses. The favorable results reported by Bakke and by Patterson follow a similar line of treatment. Pendergrass reflects the views of many persons in this country. A rather favorable experience seems to have been had with deep x-ray (Guggenheim). It is of course of the greatest importance to control the effects of radiation with frequent blood examinations, as well as observation of the clinical results, and the danger of symptoms of hemorrhage from too great reduction of platelets and leucocytes must be borne in mind. The encouraging reports of treatment by means of radiation—which in the writer's opinion is the most effective and safest form of therapy now available—must unfortunately be viewed with a certain reserve on account of the tendency of the disease to spontaneous and prolonged remissions. The choice and employment of effective therapeutic measures await the determination of the etiology of this obscure malady.

#### CONCLUDING REMARKS

The most rational basis on which to found a working hypothesis concerning the etiology of polycythemia vera takes for its starting point the remarkable and extensive hyperplasia of the red bone marrow. The polycythemia and the extraordinary increase in the circulating blood volume logically appear to be a consequence of this hyperfunction, and the pathological alterations in the circulation which they in their turn produce seem to explain very many if not all of the clinical symptoms and physical signs. The part played by blood destruction in the process, on the basis of the evidence which has been discovered to date, must be regarded as distinctly secondary.

So far as is known at present the bone marrow changes consist essentially of hyperplasia and proliferation of the normal elements, and

the gross appearance, at least, seems to suggest to most observers the state to be found in early life. It is in striking contrast, apparently, to the myeloid hyperplasia with megaloblast proliferation, described by Peabody, during the relapse in primary anemia. From all accounts, the cellular hyperplasia in erythremia shows no diminished tendency toward the differentiation of mature erythrocytic cells. Particularly in the long bones it is said that the red color is due almost entirely to the masses of mature red cells (Zadak). It is evident that the time is ripe for a reinvestigation of the histological findings by the methods and approach developed by Peabody, and by Sabin and her pupils.

There are at the present time at least two tenable hypotheses which may explain the bone marrow changes found in erythremia and it is by no means impossible that both may be of importance. The first of these hypotheses regards polycythemia vera as primarily a disease of the red marrow, strictly analogous to leukemia and with a similar etiology—a type of malignant tumor, perhaps, if leukemia is to be considered a form of malignancy. In favor of this point of view are the examples which have already been cited of “combined” or “transition” forms between the two conditions, the occasional or constant presence of abnormal red cell forms in the circulating blood, the common occurrence of evidences of increased leucocytic activity in the blood, and finally the leucemic appearances which have been found in certain reported autopsies.

The second hypothesis will regard the condition of the bone marrow as secondary to one or several different factors causing overstimulation. It will take into account first of all the fact that the essential differences existing between polycythemias of known secondary origin and so-called true primary polycythemia are often very slight indeed if considered from the standpoint of clinical signs and symptoms. It now seems quite possible that a hormonal control of bone marrow activity will eventually be demonstrated, which governs the production or maturation of blood cells. The occurrence of hormonal imbalance in polycythemia vera, as suggested by several writers (Hirshfeld especially) will then seem very likely. That this may be in part of congenital origin and due to constitutional factors, such, for example, as structural changes in the lungs, which may impede normal oxygen diffusion, is shown from the clinical reports which have

already been cited. The remarkable variation in individual reaction to known stimuli producing bone marrow hyperplasia has been emphasized above, and this can well be a question of varying individual hormonal response. It may explain the more ready susceptibility of certain individuals to the effects of emphysema or secondary lung changes, to certain infections, to alterations in the function of the liver or spleen, to abnormalities or stasis in the circulation, and to other of the many conditions which have been implicated in the production of polycythemia. Finally, it is quite possible that if such an unbalanced proliferation has once been initiated, it becomes impossible to restore the normal mechanism regulating blood cell formation even if the original disturbing stimulus is removed.

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## CERTAIN BIOLOGICAL ASPECTS OF CANCER

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### INTRODUCTION

It is impossible in a short article to cover even in a cursory manner all of the numerous studies that have been made in the subject of malignant disease during the past twenty years. In certain fields more striking advances have been made, or more interesting theories raised, and it is to these that we shall confine our attention. The problem of heredity always is of great concern to both physician and patient. The treatment of malignant disease and particularly that which has recently been advocated by Blair Bell of Liverpool, is of vital interest. A notable advance has been made in the understanding of the fundamental chemical processes of malignancy by Warburg and his co-workers, and has been confirmed by others. Gye of London has again raised the question as to whether malignant disease may not be of parasitic origin, and his work at present commands much attention. The relation of vitamins to cancer has been brought forward in recent years and much interesting work has been done along this line.

### HEREDITY AND CANCER

The existence of cancer families sometimes has been brought forward as evidence of the inheritance of neoplastic disease, as the case of the family of Mme Z, reported by Broca (1), in which 16 of 26 members died of cancer of the liver, breast, or uterus, and that of the family reported by Warthin (2) in which 17 cases of cancer (chiefly uterus or stomach) developed among 47 descendants of a cancerous parent. We must sharply distinguish, however, in such cancer families between the *congenital* tumors, such as retinal gloma, neurofibroma, and multiple enchondromata, and true *heredity* tend-



encies The congenital tumors are, of course, present at birth, they are conditioned by intrauterine conditions, and may be accompanied by other congenital abnormalities, whereas when true hereditary factors are involved these factors can be submerged completely and carried on through several generations without frank emergence Thus, the hereditary tendency to albinism in mice, or the waltzing trait of Japanese mice, may be held back without appearance for 25 or more generations, and it will remain submerged beneath the dominant character until the appropriate hybrids are again bred together On the contrary, intrauterine influences determine the congenital tumor and no submerged tendency is carried along by an otherwise healthy animal As Ewing has pointed out, the rare occurrence of a family with much cancer in it is, perhaps, an argument against the true inheritability of cancer by and large Furthermore, statistics in such a matter are always treacherous, and the study of cancer families has added but little to our knowledge of whether cancer is hereditary or not.

The statistical study of inheritance of cancer was begun by Paget (3), who found cancer in 23.6 per cent of the relatives of 254 cancerous patients, as against 18.3 per cent in non-cancerous patients Other authors (4) (5) (6) find a far smaller percentage of inheritance in their series, averaging only 7.1 per cent Hillier and Tritch (7), at the Middlesex Hospital, London, reporting on 3000 cases, found that 13.1 per cent of cancer cases had cancerous relatives, indicating that, at least in this fairly large series, heredity played no part Further, as Bashford (8) points out, the morbidity from cancer in England would lead one to the expectancy that cancer would be found in one out of every two families in the general population, and he actually found a history of cancer in 50 per cent of the families of 669 cancer patients Weinberg, from the clinic at Stuttgart (9), found no evidence of heredity in his figures Little (10), on analysis of the statistical data obtained in the family history records of the Eugenics Record Office, Carnegie Institution, found, first, that in families whose father was cancerous and whose mother was normal, there were 1717 total non-cancerous individuals and  $24 \pm 3.27$  cancerous, an excess of the observed over the expected of 22.1, and he calculates that the odds against this excess being due to chance alone would be more than

100,000 to 1. Similarly, when the immediate progeny of cancerous mothers and non-cancerous fathers were analyzed, it was found that 1030 were non-cancerous and  $39 \pm 4.13$  were cancerous, an excess of 36.22 over the expected number of cancerous individuals, 2.78 in this case. Finally, an examination of the sibs of cancerous individuals, as against those of non-cancerous individuals, showed, again, an excess of observed over expected cancerous individuals. He finds that in the general population  $1.23 \pm 0.03$  per cent are cancerous, whereas  $2.32 \pm 0.22$  per cent of the sibs of cancerous individuals have malignant disease. Little says,

"From both these sources of data it may be concluded that a tendency to the formation of cancer is clearly inherited. The influence of inheritance is shown by the occurrence of a marked excess of 'cancerous' individuals over the rate of the general population, in (1) the sibs of 'cancerous' individuals, (2) the progeny of 'cancerous' mothers by 'non-cancerous' fathers, (3) the progeny of 'non-cancerous' mothers by 'cancerous' fathers. The fact of inheritance is clear but the type of inheritance needs further investigation."

In any statistical study of the inheritance of cancer, one must remember, however, that the error in diagnosis is large, probably as high as 25 per cent, that the age span of the various individuals in the families may materially differ, and that supposedly non-cancerous controls may, of course, subsequently develop cancer. Wells (11) (12) points out the treacherous and uncertain character of statistical data insofar as they concern cancer and he would virtually discard, as useless, all existing data from this source. From clinical and statistical studies we have so far been unable to draw any definite conclusions in this matter, but it would seem advisable, according to Ewing (13), even in the face of obvious difficulties, to continue the study of human statistics, inasmuch as the transference of animal data to man is of questionable permissibility.

The early work of Bashford and Murray (14), Loeb (15), and Tyzzer (16) (17) (18), all showed that in mice there was an hereditary tendency to cancer. The most important experimental work has come from Maud Slye (19) (20) (21) (22) (23) (24) (25) (26) (27) (28) (29) (30) (31) (32). She has worked exclusively with spontaneous

mouse tumors and has, by a long and laborious study, separated out a number of homogeneous strains of animals, on which she has done over 60,000 autopsies. She concludes that, equally by the method of hybridization and by inbreeding, cancer behaves like a unit character in that it separates out and is transmitted as such. Cancer, she believes, is recessive to non-cancer, and the first hybrid generation never has shown it in all of her experience. When a non-cancer strain has once been extracted, spontaneous neoplasms never have occurred again in her series. With a double cancerous parentage, she believes that the offspring will be 100 per cent cancerous. With a single cancerous parent, the offspring will be heterozygous to cancer, in other words, they will transmit, but will not necessarily develop, cancer, and these heterozygous individuals will yield non-cancerous, heterozygous, or cancerous individuals in approximately the proportion 1 to 2 to 1. She further concludes that double non-cancerous parentage means that cancer, provided the race remains homogeneous, will never appear again.

"Resistant strains are produced which among thousands of individuals have never shown one instance of tumor of any sort, either malignant or benign. Among the susceptible mice, strains are produced which never show but one type and one location of neoplasm, such as adenocarcinoma of the mammary gland, malignant adenoma of the liver, spindle-cell sarcoma of the kidney, osteosarcoma of the leg bones etc." (31)

She points out that in her series of animals organ specificity is as marked as the simple Mendelian recessive factor of inheritance, and she believes that liver tumor begets, in the offspring, liver tumor, and that stomach cancer gives rise in the future generations to stomach cancer. Immunity to cancer, as a corollary to her conclusions, is, of course, a dominant, and although for a long time she apparently did not believe that there was any factor concerned other than the simple Mendelian recessive, she later came to the conclusion that cancer resistance and cancer susceptibility behave consistently, just as true albinism or pigmentation do in heredity and, that two factors are necessary for the production of cancer, first, an inherited local susceptibility to the disease, and, second, an irritation of the right kind and in the right degree (31).

She says (28),

"The fact that various types of irritation play an important part in the causation of cancer in susceptible individuals is one of the best basic arguments for defining cancer as an abnormal regeneration process. This regeneration after trauma is apparently abnormal in these cancer-susceptible subjects because of the lack of a differentiating mechanism in the tissues. It seems to be this local lack of differentiating mechanism in the susceptible tissues that is the hereditary element in cancer susceptibility. That is, the type of local response made to a given type of irritation is determined by heredity whatever the type of that irritation may be."

She objects to the use of transplantable tumors, such as have been used by some workers in the field, and she points out that the susceptibility to grafted tumors has as its most important bases, first, the ability of the assaulted tissues to regenerate normally, second, the ability to build up an accessory circulation, and, third, strength on the part of the host to support the tumor. She believes that transplantable tumors are the exact opposite, in their genetic relations, to spontaneous cancer, in which the tendency of the assaulted tissues is to regenerate abnormally in an uncontrolled and undifferentiated manner. She sees, therefore, no contradiction in the fact that, whereas she has found cancer to be a simple Mendelian recessive, most workers in the field of grafted tumors find that these behave as a dominant, though not, in most cases, as a simple dominant.

To Slye's work Cockayne (33) objects (in so far as the mammary carcinoma is concerned) that in most cases

"she has used in generation after generation a mouse with carcinoma of the mammary gland as one parent, and although she proves, in this way, beyond doubt, that the tendency to cancer is inherited, she does not prove that it is inherited as a recessive. She regards these crosses as crosses between a mouse homozygous for, and one heterozygous for, mammary carcinoma, but the same result would be obtained if the tendency to carcinoma were dominant, and the cross were between a mouse heterozygous for the condition and one homozygous for the normal."

Cockayne concludes that "She (Slye) has been dealing with three hereditary disorders, each one due to a separate unit character and consequently inherited independently." These disorders (according to Cockayne) are

"adenomatosis of the lung and of the liver, which are probably recessive, and adenomatosis of the mammary gland, which is probably dominant. Malignant disease develops in a comparatively small proportion of the first two, and in a very high proportion of the last of these In the case of tumors of mice, Slye produces no complete proof that they are inherited, though her pedigrees suggest that some behave as Mendelian recessives and others as dominants "

Wells (11), on the other hand, agrees in general with Slye's results, but he is not entirely convinced that these figures and theories can be transferred to the human race Little (34) says,

"In the interpretation of her data, however, there is room for grave disagreement in her conclusion that cancer behaves as a simple Mendelian recessive Even admitting the difficulty introduced by occurrence of cancer at an advanced age in the lifetime of an individual and the limitation of the most common class of tumors due to sex (mammary carcinoma), it is still evident that a simple type of Mendelian inheritance does not fit the observed facts sufficiently well Furthermore, the fact that certain families of mice show such a higher incidence of neoplasms located in a particular locality indicates that subsidiary or modifying factors are influencing the situation and in all probability the occurrence of neoplastic growths "

Little agrees that it has been proved beyond question that heredity factors play an important part in the determining of the incidence of cancer in mice but he feels that though the fact of inheritance is undoubtedly established, the method of inheritance is not yet determined He (35) expresses the "hope that great caution will be exercised by those reading the interpretations of these two investigators (Slye and Wells) before accepting their conclusions that cancer is a simple Mendelian recessive." He believes that Lynch (v i) is correct in her contention that mammary cancer in mice behaves like a Mendelian dominant—a conclusion directly opposite to that of Slye It is possible and permissible to argue the existence of hereditary tendencies of cancer in man from the existence of such tendencies in other animals Similar arguments have been shown to apply in such abnormalities as albinism and color of the eyes, but Little emphasizes the extremely complicated biological nature of

cancer, occurring as it does in middle life or old age, at a point very far removed from the carriers of the elementary hereditary tendencies, and the opportunity for the effects of internal environment to become excessively complicated and amplified are, of course, obvious. As regards inheritance in man, he points out that one is faced with inadequate methods of observation, diagnosing, and recording, the magnified effects of environment due to the long life cycle, and small numbers of young, and a deliberate system of out-breeding which confuses the situation. All these factors make the study of inheritance of cancer in man very difficult.

Bagg (36) found that he could increase the per cent of cancer of the breast in an inbred strain of mice with a normally low tumor incidence by such environmental changes as rapid breeding, and he concludes that heredity is not the only important factor in the production of tumors. Slye (28) contends that his mice were heterozygous to cancer and that, therefore, the amount of cancer in any group of descendants would depend upon what matings had been made, and she implies that the rise of tumor incidence which Bagg found was due to the "right selection of breedings."

More recent work of Murry (37) confirms, however, the fact that environmental changes do alter the tumor incidence in mice. He found, for instance, that enforced non-breeding "delays very markedly the age of tumor incidence and may even inhibit entirely the development of cancer in mice which would have had a high incidence of tumor appearance had they lived a normal sexual life." Furthermore, the complete absence of ovarian secretion (castration) was found to have much the same effect on cancer incidence as did enforced non-breeding. Once more, from these data it would appear that factors other than heredity have a marked influence on tumor incidence.

Loeb and Lathrop (38) (39) (40) (41), working with spontaneous tumors, found that it was possible to split a strain of mice into sub-strains with varying tumor incidence. In the majority of cases, isolated families inbred through several generations gave approximately the same tumor rate, the observed variations perhaps being due to the small number of animals used. They conclude that, on the whole, the heredity of cancer rate and cancer age follows the

blending type of hereditary transmission, and, in crossing strains which differed in their tumor incidence, no general rule was found by which one could predict the rate in the offspring. In a certain number, the results were undoubtedly intermediate. All kinds of gradations were found to occur, leading, on the one hand, to preponderance of strains with a high rate and, on the other, to a preponderance of those with a low rate. Multiple allelomorphs, they believe, determine the heredity to cancer, and their results make these authors feel that multiple factors rather than a single one are involved. It has been objected that the strains of mice used by Loeb and Lathrop were not homogeneous, and that the hybridization results were therefore not valid. The data do show, however, that multiple factors are involved.

Guerin (42) concludes that multiple factors are involved and he does not believe that simple heredity will explain all the observed facts. Wilson (43), working with *drosophila*, also feels that multiple factors are involved. Wilson found two hereditary tumors in the fruit fly, but he was unable to be sure whether the tendency was dominant or recessive. Lynch (44) (45) in a study of tumor incidence in inbred and back-cross daughters, supports the theory that the tendency is hereditary, and the frequency in the first generation would indicate, contrary to the results of Slye, that this tendency is dominant. Cockayne (33) agrees that Lynch's results point strongly to the conclusion that the tendency to cancer behaves in this manner. Lynch (46) found further that tar gave the same incidence of tumors in races with a high and low spontaneous tumor rate. Slye, however, objects again that her strains were not homozygous to cancer and that the cancer percentages will depend entirely on what matings are made. She further points out (28) that Lynch used both males and females in her tarring experiments, whereas she has given the cancer incidence for the females only.

In summary, it seems fair to say, as Little has said, that the fact of inheritance in animals has been definitely proved, but that even here we are not positive of the exact mechanism of the inheritance. The transferal of these data to man, while permissible in part, becomes so complicated by such multiple factors as age span, and out-breeding that it is very difficult, if not impossible, to say what influence, if any heredity has in cancer to man.

## THE PARASITIC THEORY OF CANCER

The parasitic theory of the origin of malignant disease has been brought up many times in the past. A considerable number of investigators (47) (48) have asserted that this or that microorganism was the true cause of cancer, but none of these claims has so far been substantiated (13). It has been shown without doubt by Fibiger (49) that cancer of the stomach may develop about encysted spiroptera. Similar observations have been made by Bullock and Curtis (50). In these instances, however, we are dealing with a chronic irritation factor and not, of course with any specific organism that might be of etiological importance in human cancer. Numerous authors, more recently Blumenthal (51) (52) and Nuzum (53) (54) have claimed to have isolated from animal and human cancer organisms with which they were able to reproduce malignant disease of a similar sort in experimental animals. Blumenthal asserts that he has cultivated from human neoplasms three strains of bacteria which produced, in rats and in mice, neoplasms which could be further transplanted. It is noteworthy, however, that the takes were few in number and that he was unable to cultivate the organism from these transplants. Their work, moreover, has not been confirmed.

More recently the work of Gye (55) (56) (57) (58) has attracted much interest. Gye's theory, in brief, holds that all tumors are caused by two factors, a non-specific filtrable virus, common to all tumors, and a specific chemical substance which renders certain tissues susceptible to the virus and enables the virus to produce the lesion. His work has been done largely with the Rous chicken sarcoma.

In 1911 Rous (59) described a new sarcoma of fowls which could be propagated from chicken to chicken by a cell free filtrate, though it was found impossible to transfer it to mammals even by using living cells. Other filtrable tumors were subsequently (60) found by Rous, but all were specific for fowl. It remained true, therefore, that no mammalian tumor was filtrable, so that doubts have been raised as to whether the Rous' sarcoma is, indeed, a true tumor in the usual sense of the word, though it may be argued that it has all the usually accepted criteria of malignancy and that the mere fact of its filtrability should not militate against these facts. Rous himself was non-



committal as to the nature of the "agent" by which the tumor was propagated. He hesitated to call it a virus, but he and his collaborators showed that it was destroyed by a temperature of 55°C. for fifteen minutes and by chloroform, toluene, and phenol.

Gye's experimental evidence, in brief, is as follows. The virus from the Rous chicken sarcoma is obtained by grinding the tumor, after excision under strict aseptic precautions, with sand. Saline is added and the suspension filtered through sand until clear. This process yields the so-called "sand filtrate," which is capable of infecting fowl in doses as small as 0.05 ml. The active agent, or virus, in this filtrate may be killed by various agents (61), but Gye originally (56) used "a few drops of chloroform." After such treatment the "sand filtrate" is usually innocuous, even in doses as large as 2.0 ml. If, on the other hand, a small piece of tumor tissue be incubated for from 2 to 7 days in modified Hartley's broth under anaerobic conditions, this so-called "primary culture" also becomes non-infectious. A combination, however, of "sand filtrate" and "primary culture," neither of which alone will, *as a rule*, produce a tumor, will result in tumor. Gye's assumption is that there are two factors—a living virus and an accessory chemical substance. In experimental tumors produced by the combination of these two factors the former is contained in the "primary culture" and the latter in the "sand filtrate." Since the virus can be furnished by small amounts of sub-cultures of tumor tissue in modified Hartley's broth, as high as the fourth or fifth generation, the resulting dilution of the tumor would seem to be sufficiently great to rule out mere survival of the agent. And, since the virus factor may be obtained from rat tumor No. 9, Jensen rat sarcoma, mouse carcinoma 63 and human carcinoma, it is assumed that it is present in all malignant growths and, hence, non-specific. The accessory chemical substance, on the other hand, is specific and determines the type of tumor. Gye assumes that the "chloroform treated sand filtrate contains a labile chemical compound which in some way, as yet unknown, renders the cells susceptible to infection by the virus contained in the "primary culture."

A second line of evidence is seen in the following. A suspension of tumor tissue, incubated anaerobically at 39°C., is spun down at a

high rate of speed, the supernatant fluid is removed and the sediment thoroughly washed with saline. Neither the supernatant fluid nor the washed sediment will alone produce a sarcoma, but when they are combined a tumor results. These experiments "show that both in primary cultures and in candle filtrates there are two factors which are necessary to the production of tumor—the one is particulate and is therefore probably a virus, the other, being uninfluenced by spinning, is probably a chemical substance" (55).

There are two points in relation to Gye's work which demand serious consideration. In the first place, he has been able to recover the specific chemical substance from only one type of tumor, namely, Rous' chicken sarcoma—a tumor which may not be a true tumor in the usual sense of the word. Furthermore, as he reports occasional "takes" with the specific chemical factor only, in amounts which are comparable to those used in experiments on which his theory is based, the point as to whether the original infective agent of the "sand-filtrate" has been killed or not is debatable.

His co-worker Barnard (62) believes that he has photographed the virus by ultra violet ray, but the technical difficulties involved make it difficult to repeat this work.

Many objections, aside from the choice of tumor, have been raised against Gye's theory. Murphy (63) (64) was able to reactivate the chloroform filtrates by embryonic and by normal tissue, and he concludes that there is no necessity for the assumption of a living virus derived from tumor tissue. Flu (65) (66) has come to the same conclusions. McKenzie and Illingsworth (67), however, were not able to reactivate with embryonic or normal tissue, and they believe that their work supports that of Gye. They were, however, unable to subculture the virus as Gye had done. They were able to replace the virus from Rous chicken sarcoma by an agent from mouse carcinoma 63, but not from mouse sarcoma 37. But they further state that "We have not been able to produce the Rous sarcoma from subculture and 'specific factor' in any instance where the specific factor alone did not likewise bring about a growth." They believe that the "specific factor is in reality nothing more than a suspension of attenuated virus which may or may not produce a tumor, depending on the fowl's susceptibility or resistance." Further observations

on this point must be made before the objection can be considered entirely vitiating Gye's theory

Harkins and others (68) have found that, if a large amount of chloroform be added to the virus, it will be killed entirely, but that a few drops, as recommended by Gye, failed to destroy the virus in 25 per cent of the cases. In fact these authors still obtained frequent "takes" even when using 2 per cent chloroform. It should be noted, however, that Gye's "sand filtrate" must be absolutely clear if chloroform is to act in a consistent manner, and not all investigators have paid sufficient attention to this point.

Mueller (69) concludes,

"We have absolutely no indication of the necessity of two factors in the production of the Rous sarcoma. Because of the conflicting nature of the results obtained by those who have undertaken to repeat the work, and on account of the difficulty of controlling all factors involved, we do not feel that it may be stated definitely that Gye's theory of the cause of cancer is wrong."

Baker and McIntosh (70) find marked variation in the infectivity of the filtrate from Rous sarcoma, and they show that this variability is due to those factors which control ferment action, especially the hydrogen ion concentration. They suggest that "the discrepancies between the results of different workers upon the Rous sarcoma, particularly in relation to Gye's work, can be accounted for by a lack of control of" these factors. Cutler (71) again was unable to confirm Gye's work. He concludes that the susceptibility of the Rous tumor filtrate to chloroform varies to such an extent that proper standardization of this technic is not possible.

Further work must be done before this theory can be proved or disproved, and it is too early, at present, to give a final opinion. There is no doubt, however, that many new facts of importance and interest will come from the experiments, no matter what the actual outcome is.

Finally, it should be remembered that there are numerous theoretical objections to the parasitic theory of cancer. The incidence, course, age distribution, and anatomical character of the disease is against such an assumption. Ewing (13) says (in part),

"The anatomical and physiological characters of malignant tumors differ essentially from those of known infectious processes. The abnormal size of nucleus and cell body revealing overnutrition is contrary to the rule in infectious processes. The metastases of tumors reveal conditions wholly different from any phenomena observed in infectious diseases. There is no more impressive illustration of the difference between tumors and infectious granulomas, which they most nearly resemble, than the comparison of the fate of tumor emboli and of emboli from a tuberculous focus. In the former case the tumor cells grow where they lodge, receiving only nutriment from the blood of the part, in the latter case the embolic cells die and the transported bacilli excite an inflammatory process in the adjacent tissues.

Tumors arise in some instances from a single cell, in most instances from a narrowly circumscribed group of cells, and grow chiefly or exclusively from their own resources. Few writers have ventured to suggest that benign tumors can be of parasitic origin, and yet occasionally tumors which are otherwise indistinguishable from benign growths, as adenoma of the thyroid and leiomyoma, may exhibit all the characters of malignancy. Hopeless dilemmas arise when one attempts to conceive of all the necessary properties of the cancer parasite."

And Ewing concludes,

"It is impossible to regard as a valid hypothesis the conception of a specific group of parasites living in symbiosis with the cancer cell and stimulating its growth and nutrition. All the facts are reasonably explained by regarding the cancer parasite as the cancer cell."

#### ACCESSORY FOOD FACTORS AND CANCER

The relation of accessory food factors or vitamins to malignant disease very naturally has come to the attention of workers in this field in recent years. The most interesting investigation in this relation is that of Burrows (72) (73) (74) (75) (76) (77) (78) (79) (80) (84). He believes that the neoplastic changes which cells undergo are due to the environment in which these cells reside, rather than to any specific organism or specific changes in the cells themselves. Cancer, according to him, is not a reversion to the embryonic type of cell but a freeing from controlling environmental forces. Growth, differentiation, and function he regards as determined, not by the cells themselves, but by their immediate surround-

ings The view that cancer cells are capable of independent growth under conditions other than those favorable for the growth of normal cells he believes to be false. His early studies were made on tissue cultures and he finds that

“embryonic mesenchyme . . . in a tissue culture, first invades the medium, then grows, and finally suffers a self digestion, exactly as cancer cells suffer these changes in the body. These reactions are not reactions of the cells to specific substances in the plasma. They are the result of the removal of these cells from the normal circulation of blood in the organism to a stagnant culture medium that is well supplied with oxygen.”

They are, according to Burrows, the result of a gradual accumulation in this stagnant environment of a substance which he names the archusia. This so-called archusia he believes is formed by the cells themselves and only in the presence of oxygen. In low concentrations ( $S_1$ ), the archusia has no effect on the surrounding cells. In medium concentrations ( $S_2$ ), it causes the cells to migrate into a solid medium and toward such droplets of fat as may be in the vicinity. In high concentrations ( $S_3$ ), of the archusia, the proteins and fats are digested, and the cells grow and divide by mitosis. In all higher concentrations ( $S_4$ ), the cells themselves are digested. The concentration of archusia is directly proportional to the number of cells acting per unit area, the nutrient substances and the oxygen present, and inversely proportional to the amount of medium diluting it. Burrows also assumes the elaboration of a second substance, a product of cells in the presence of oxygen—a fat soluble substance which he calls ergusia. This substance reduces surface tension and coagulates fibrin and so aids the cells in migrating to distant parts, but in turn it retards the growth of cells just as “archusia” aids their growth. From these studies of tissue culture Burrows was led to believe (77) that cancer is due to a local crowding of cells and a relative reduction in the blood supply of the mass.

His co-worker, Jorstad, points out (78) that coal tar and other liquid fat solvents produce cancer or pseudo-cancer, not by any stimulating action that they may have, but rather by drawing the cells together into a compact mass due to the extraction from the cells of the ergusia. Animal parasites, likewise, cause a dense mass

of cells to accumulate and these suffuse their own archusia and thus produce a local condition favorable to the proliferation of cells already crowded together. Radium and x-ray disturb the vascular supply and increase the production of archusia. Burrows shows (72) (80) that a dense mass of cells destroys any neighboring less dense mass of cells, just as cancer destroys the normal tissues about itself.

He points out (79) that in tissue culture cells grow only when they are crowded together, and that, if a stream of fresh serum be passed over the tissue culture, growth and function cease, because, as he believes, the serum soluble archusia is washed away. The per cent of this substance Burrows finds to be high in embryonic tissue (81), and he points the parallel of this fact to the observation of Robertson (82), that the rate of growth of paramoecia is directly proportional to the number of individuals per unit volume of medium until the medium becomes charged with waste products above a certain concentration. In short, Burrows believes that two substances in the environment govern the growth and activity of all cells—first, the archusia, water soluble, which allows cells to grow, differentiate and function, and second, ergusia, fat soluble, which acts as a restraining force upon the unlimited and chaotic increase of cells by themselves—and that cancer is due to any process which upsets the balance by causing a relative increase in the concentration of archusia.

So far Burrows contributes little over and above the school of investigators which believes that cancer is due to an imbalance between a growth promoting and a growth retarding agent. He takes a material step forward, however, in his proposed identification of archusia with vitamin B and of ergusia with vitamin A. This ergusia, he believes, is a product of growth reaction and inhibits growth, not as a foreign toxic substance, but, as any product of an incomplete reversible reaction may inhibit the reaction when added in excess to the reacting system. In support of this rather striking view that these substances are really vitamins he brings forward a certain amount of evidence.

In the first place, he finds that both vitamin B and archusia are plentiful in embryonic tissue, and that both reach their maximum concentration in a chick of five days (76) (80) at which period the

growth rate is at its fastest. This growth rate decreases as the embryos age and in a similar fashion the contents of both vitamin B and of archusia decrease (75) (84). In like manner extracts of cancer cells cause tissue cells to grow very rapidly at first and then to disintegrate. An analogous growth stimulus and later disintegration is brought about by extracts of five day embryo. He considers that he has shown (73) (84) that cancer tissue (Jensen sarcoma) is high in vitamin B but his protocols do not appear to prove this with certainty and experiments conducted in this laboratory, but as yet unpublished, indicate that carcinomatous tissue has no higher vitamin B content than normal non-active tissue. Burrows concludes, however (84) that

"This high vitamin B value without any noticeable vitamin A is seen not only in actively growing tissues of the body (embryo) but also in the culture of the actively growing tumor forming organism *B. tumefaciens*. While it is impossible to prove without working with pure products that the archusia (S) of the cell is vitamin B, there is no evidence from these experiments that it is otherwise. Our test for the archusia is the ability of a cellular exudate to stimulate activity in tissue cells. The highest stimulating extracts are obtained from the most actively growing cells, cancer, young embryos and actively growing young cultures of bacteria. These have been found to have the greatest amount of vitamin B."

It is interesting in this respect that Heaton (94) found that the requirements for growth of different tissues were not the same and he described these separate factors concerned with the growth and multiplication of fibroblasts and epithelium. One of these is a thermostabile substance necessary for the multiplication of epithelial cells. This factor he finds to be water soluble and abundant in yeast, and he regards it as very closely associated if not identical with vitamin B. Thus from an independent worker comes a certain amount of confirmation of Burrows' proposed identification of archusia with the growth promoting vitamin.

Burrows further regards the "fat soluble ergusia" as having the general properties of vitamin A (84). He finds that the ergusia lost to cells can be replaced by vitamin A and from this and other lines of evidence he concludes that vitamin A is "present as the ergusia in

the intercellular substances in higher animals and in their stored fat " Vitamin A (or ergusia) he regards as formed during the growth reaction of cells and he believes that it must "slow the growth reaction of the cell" as does the product of any essentially reversible reaction

Burrows believes, in short, that cancer is merely the result of anything which locally removes vitamin A from the tissues or locally increases vitamin B X-ray causes cancer, according to this theory, by increasing the local amount of vitamin B and Burrows shows that animals on a vitamin B free diet will live longer if small doses of X-ray are given them Parasites produce cancer—when they do—by their liberation of large amounts of vitamin B Tar produces malignant changes by locally depleting the tissues of vitamin A and Burrows shows that animals killed by tarring can be saved by feeding large amounts of A Chronic irritation with scar tissue tends to produce cancer by reducing the blood supply and allowing the archusia, or vitamin B, to accumulate Burrows substitutes stagnation for chronic irritation, just as Warburg with somewhat less enthusiasm substitutes anoxemia for chronic irritation

It is most difficult, on this basis, to explain the existence and behavior of metastasis, but he does so by assuming that the cells migrate out along the drainage areas from the original focus and reach eventually a place in the body where growth is possible simply because the environment is suitable He believes that the fat and protein soluble ergusia is liberated only when the archusia has reached an  $S_2$  concentration The ergusia forms a film which reduces surface tension and along this the cells may migrate Evidence that some active substance proceeds from the cancer focus Burrows finds in the observation made some years ago by Ewing, that lymph nodes adjacent to malignant deposits may show, without actual metastatic nodules, marked hypertrophic changes It would seem, however, that according to theory this hyperplasia should result from action of archusia rather than of ergusia

The natural consequence of this theory, which is at least interesting, is that one should be able to modify the course of malignant processes by vitamins or other accessory factors Much work has been done on this aspect Sugiura and Benedict (83) found that absence of vitamin B from the diet had no effect on the tumor growth in ani-



imals Wyard (86) was unable to demonstrate any effect when vitamin A was absent Lapidari (87), however, felt there were less tumor takes in transplantable chicken tumors when the diet contained no vitamin B, and Ludwig (88) saw no tumor takes out of 60 animals on a vitamin free diet, as against 57 takes out of 60 control on normal diets Kramer (89) found that absence of vitamins neither hindered nor accelerated the growth of animal tumors, while an excess of vitamins made the tumors grow more rapidly. Fujimaki (90), feeding rats a diet containing no vitamin A, found, as others have done, that there was a hyperplasia of the epithelium of the stomach, which he interpreted as carcinoma Wolbach (91) (92) has amplified this work and found similar results but is not prepared to call the change carcinomatous Goldblatt (93) comes to essentially the same conclusions Most attempts to alter the course of cancer by dietary means have consistently failed but this does not necessarily imply that they always will

#### THE CHEMISTRY OF MALIGNANT DISEASE

Ever since 1836 when Johannes Muller (95) sought to isolate a specific chemical substance from carcinoma, the interest in the chemical make-up and chemical behavior of malignant disease has increased. Many able chemists have worked on the problem, and from time to time substances have been isolated which were said to be characteristic of new growth, but this has subsequently been shown not to be the case A careful chemical examination of carcinomatous tissue fails to show any substance to which the properties of malignancy might be attributed (96) (97) (98).

Certain phases of the elementary analysis of neoplastic tissue are, however, of considerable interest E Freund (99) as early as 1889, and Joanovics in 1916 (100) showed that malignant tissue presented certain anomalies in its carbohydrate make-up, and the recent work of Warburg has elaborated this field into one of the most important in the metabolism of neoplasms This aspect will be discussed in detail later.

The salt content of the fluid bathing tissues is of the utmost importance to proper growth and function as has been particularly emphasized by Loeb (101), and it is to be expected that variations

from the normal in the mineral content of tumors should be sought for. The narrow limits within which the fluids can be varied without injury to the cells is striking. The calcium content of tumor tissue has been shown to be low, particularly in the early stages of carcinoma, though it may rise when the tumor becomes older or necrotic (102) (103) (104) (105). Conversely, potassium is generally conceded to be increased in tumors (104) (106). And it is to be remembered that calcium and potassium are mutually antagonistic in so far as their physiological effects are concerned (107). This finding of a low calcium and a high potassium led to the study of the K/Ca ratio, and Clowes and Frisbie (103) consider that this ratio is a function of the age and condition of the tumor, increasing in value with increasing rapidity of growth on the part of the tumor and their general conclusions receive confirmation from Rhodenburg and Krehbiel (108). It is interesting in this respect that Sugiura and Benedict (105) found that calcium had a slightly retarding action on the growth of rat cancer, and Cramer (109) found a similar effect.

The diamino acids have been shown to be high by Drummond (110) and by Bergell (111), but the significance of this finding is slight. The water content of neoplastic tissue is elevated, as with other rapidly growing tissues (112) (113). Waterman (114) gives the water content of human tissues as 77.5 per cent for normal tissue, 81.6 for malignant tumors.

The lactic acid content of malignant tissue is generally considered to be raised over that of normal tissue (115) but the values interlock with those of normal tissue and what rise there is, is not particularly striking (115) (116). Bierich gives the lactic acid content of various normal organs as from 23 to 140 mgm per 100 ml and for tumor tissue 112 to 258. It should be remembered, however, that the determination of lactic acid in tissue is not on an entirely sound technical basis, and further work is needed before we can say exactly what the lactic acid content of tumor tissue is.

Much interest has arisen in the per cent of the dipeptid, glutathione, in cancer inasmuch as this substance has recently been shown to have a very profound influence on the oxidation and reduction processes in tissues in general. The question of whether glutathione content is normal or abnormal in tumor tissue can not at present be decided.

Yaoi and Nakahara (117), using the nitro-prusside test, have claimed that glutathione is present in the Rous chicken sarcoma only in negligible amounts, whereas they find it abundant in other malignant tumors and in normal tissue. Hieger (118) finds, however, that Rous chicken sarcoma contains approximately the same amount of glutathione as do normal tissues. On the contrary, Holmes (119) using Tunnichliff's method (120) for reduced glutathione, estimates that whereas liver contains 200 to 300 mgm per 100 grams wet weight and muscle 35 mgm, cancer often contains less than 3 mgm of glutathione and never more than 16.5 mgm. The determinations in this case were done by the iodine titration method on the reduced form, but it was also shown that cancer could not reduce added glutathione. Holmes' conclusions are that rat carcinoma, rat sarcoma, and human carcinoma contain very small amounts of reduced glutathione, and that cancer, unlike normal cellular tissue, appears also to show only a slight activity in reducing added oxidized glutathione. She believes that these facts lend support to Warburg's contention that cancer lives essentially in an anaerobic manner. Hopkins (121) says that actively growing cancer cells show a low nitro-prusside test, but he did not examine fresh tissues soon after removal from the body, and the work is open, therefore, to some theoretical objection. Voegtlin and Thompson (122) find, in contradistinction to these other authors, that glutathione is as abundant in malignant transplantable mammalian tumors as in liver, which they find very rich in this substance. The necrotic proportions of the tumor contained no glutathione. But they believe that tumors contain more of the oxidized (S-S) form than normal tissues. They further find that the glutathione is drawn from the body by the tumor inasmuch as the content of the body as a whole diminishes as the tumor increases in size. They give for liver 135 to 261 mgm per 100 gm., and for cancer 0 to 117 mgm per 100 gm with an average of 50. They find that 95 per cent of the glutathione is in the reduced form.

Hieger (118), estimating by Tunnichliff's method the glutathione, concludes that the glutathione content of normal and neoplastic tissue is essentially the same. Bierich and Kalle (123) show that the absolute glutathione content of tumors fluctuates markedly. The

subject is therefore in a somewhat chaotic state and more work is needed before a definite answer can be given to the influence of glutathione on cancer

Much recent work has been done on the reaction of tissue cells in general and malignant cells in particular. The pH of the blood in cancer does not materially differ from normal (124) (125). Chambers and his associates (126) have recently shown that the pH of normal tissue varies from 6.9 for the cytoplasm to 7.5 for the nucleus. Woglom (127) determined the pH of various tissues and finds that, whereas muscle is 6.31 and subcutaneous tissue 7.05, the Flexner-Jobling rat carcinoma showed a pH of 7.11 and the Crocker rat sarcoma No. 10 a pH of 6.95. Harde and Danysz (128), using Rous' vital staining method, conclude that the pH of mouse sarcoma S 37 and mouse carcinoma 63 lies between 5.8 and 6.2. If this work can be confirmed, and if the reaction of tumor tissue is actually below 6, it would be of very great interest in view of the fact, which will be discussed later, that the glycolytic power of malignant cells, and in a sense, therefore, their ability to live, ceases at approximately this point.

Blair Bell and his associates (129) (130) (125) find that the phosphatid content of malignant tissue is raised and that the phosphatid-cholesterol ratio is higher in neoplasms than in normal tissue, and he points out that, whereas cholesterol favors a type of emulsion in which the internal phase is water, phosphatids favor a type of emulsion in which the external phase is water, and of course this latter phase system greatly facilitates the passage, and hence the availability, of nutrient substances. The same increase in permeability is favored by a low calcium (131) such as is found in actively growing cancer. This observation of a disturbed phosphatid-cholesterol ratio, however, remains to be substantiated. Certain other physicochemical variations from the normal have been observed (132) (125) but their practical significance is not entirely clear. The electrical conductivity of cancer tissue has been shown to be increased (133) (134) (135). Grant (135) has shown that the conductivity of tumor tissue approaches that of N/10 HCl. Fricke (136) does not find a consistent increase in the conductivity, though he finds the electrical capacity increased in all cases.

been obtained in this laboratory that the acids mentioned by Freund and Kaminer are not toxic in vitro for mouse carcinoma.

The most interesting work of recent years in the chemistry of carcinoma has come from the laboratories of Warburg (153) (154) and his associates (155) (156) (157) Warburg (158) in studying the gaseous metabolism of sea urchin eggs, noted, as others had done, that their oxygen consumption was very large, increasing, as it does, six times at the moment of fertilization. Inasmuch as carcinoma is a rapidly growing tissue with some superficial resemblances to the embryonic state, Warburg studied the metabolism of the Flexner-Jobling carcinoma and found, much to his surprise, that living cancer cells did not use up much oxygen, in fact, they used very little. In an effort to overcome what he believed to be a technical error, he added sugar to the fluid medium in which his experiments were being made, and there then developed the fact, which has since been substantiated, that carcinomatous cells destroy sugar with great rapidity, either under anaerobic or aerobic conditions. It is on this general fundamental thesis that Warburg and others have evolved a working classification of various tissues which marks off malignant disease as a type of growth differing on the one hand from normal adult tissue, and on the other hand from rapidly growing embryonic tissue Warburg's determinations (159) (160) (161) were made, in brief, by placing very small, very thin, bits of living carcinomatous tissue in a suitable chamber (essentially a modified Barcroft differential manometer) containing a modified Ringer solution with sodium bicarbonate and dextrose. The evolution of any acid in this medium will, of course, give rise to carbon dioxide which can be measured manometrically This gas, therefore, serves as a quantitative indication of the amount of acid formed The method is relatively simple and accurate By it Warburg has found that cancer tissue destroys approximately one-tenth of its dry weight of sugar each hour, and that it transforms this sugar into lactic acid

Inasmuch as the fundamental metabolic processes are an expression of the mode of life and growth of any tissue, it is by the qualitative and quantitative estimation of these processes that we may hope to arrive at an understanding of just what cancer is and how it behaves Pasteur first drew attention to the fact that some organisms live

aerobically and others live anaerobically, yet at the same time he pointed out there was no fundamental difference between these two modes of life, and we are daily coming more to an understanding of the degree to which the tissues of higher organisms do—or can—live under anaerobic conditions Meyerhof (162) has shown that muscle in contracting derives its energy from the hydrolysis of sugar We have, therefore, two large sources of energy (and hence life) in tissues, first, the aerobic combustion of glucose to carbon dioxide and water, and, second, the anaerobic glycolysis of dextrose to lactic acid It is the relative proportion of these two sources of energy of tissue that Warburg has concerned himself with

Certain definite facts have been brought out The anaerobic glycolysis of tumors and other actively growing tissues is far more rapid than that of less active normal adult tissue Cancer tissue splits not only glucose but also galactose, fructose, and mannose The amount of glucose transformed into lactic acid, and hence to energy, obtained by the tumor depends (a) upon the temperature, increasing with rising temperature, (b) upon the glucose content, rising again with rising glucose content, and (c) upon the pH of the solution, the glycolysis reaching its maximum at a pH of about 7.8, and diminishing to almost a vanishing point at a pH of 6 Cancer tissue, therefore, with its formation of 10 per cent of its dry weight of lactic acid per hour, produces 100 times as much as blood, and 200 times as much as the resting frog muscles, and still 8 times as much as a fully acting frog's muscle

The presence of available oxygen in an experimental medium depresses the glycolytic rate in all types of tissue, but it does so most markedly in the case of normal adult tissue, where aerobic glycolysis is practically wanting When, therefore, tissue is transferred from anaerobic to aerobic conditions, we find that, if the velocity of the splitting process is great and the respiration slight, then, on transfer to aerobic conditions, a greater part of the glycolysis will still go on If, on the contrary, oxidation is great in comparison to hydrolysis, then the latter will cease to a large extent in the presence of available oxygen Yeast with its low oxygen consumption behaves in the first way, muscle with its great oxygen consumption in the second With muscle, transference into an oxygen containing medium brings about

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a virtual cessation of hydrolysis With yeast and with cancer cells, on the contrary, transference to an oxygen-containing medium has but little effect upon the magnitude of the hydrolytic change, for the respiration of cancer tissue is too slight to influence materially its power to split, by hydrolysis, glucose into lactic acid Under anaerobic conditions, in benign tumors, the glycolysis is of the same order of magnitude as with malignant growths, and we have therefore an indication that there is no great fundamental difference between malignant and benign tumors; but, under aerobic conditions, the difference becomes more marked and malignant tumors produce three or four times as much lactic acid per molecule of oxygen consumed as do benign tumors. Embryonic tissue, under anaerobic conditions, produces lactic acid in large amounts, in fact, as much as does tumor tissue; but, as we have noted above, the consumption of oxygen is very large in embryonic tissue and, consequently, the transference to a medium containing available oxygen results in the almost complete disappearance of the hydrolytic change The respiration of normally growing tissues again suffices to bring about a virtual disappearance of the glycolytic products If one calculates the number of molecules of lactic acid whose production has been inhibited by the consumption of one molecule of oxygen, one finds that for both normal and cancerous tissue this value varies between 1 and 2, and it is obvious, therefore, that each molecule of oxygen consumed prevents the hydrolysis of from 3 to 6 molecules of dextrose. Meyerhof has shown that the same relation holds in the case of muscle. Now, if we calculate from observed figures the amount of energy obtained by oxidative mechanism on the one hand and hydrolytic processes on the other, we find that nearly 40 per cent of the total energy of a tumor may come from the glycolytic process alone And it has been shown by Okamoto (163) that both the Rous sarcoma and the Jensen rat sarcoma could be kept alive and viable under aerobic conditions, and Wind (164) has succeeded in cultivating Rous sarcoma in the virtual absence of oxygen The cancer cell, it would seem, does not need oxygen

That the same marked glycolysis actually occurs *in vivo* has been shown by Tadenuma (165) and by Cori (166) who observed that blood passing through a sarcomatous wing of a fowl lost more sugar than

that passing through a normal wing This observation has been amplified by Warburg (167)

As regards the classification of cells, Warburg points out that normal adult tissues show a high rate of oxygen consumption and but little glycolysis, while embryonic tissue shows both high respiration and high glycolysis under anaerobic conditions, but only slight glycolysis under aerobic conditions, and neoplastic tissue has a rather low respira-

TABLE 1

TISSUE	AEROBIC GLYCOLYSIS	ANAEROBIC GLYCOLYSIS
Normal	Slight	Slight
Embryo	Slight	Great
Tumor	Great	Great

TABLE 2

TISSUE	QO <sub>2</sub>	Q <sub>m</sub> <sup>N<sub>2</sub></sup>	U
Rat kidney	-21	+3	-39
Rat liver	-12	+3	-21
Rat spleen	-12	+4	-20
Rabbit pancreas	-5	+3	-7
Dog pancreas	-3	+4	-2
Rat embryo (3 mgm )	-12	+13	-11
Hen embryo (1 7 mgm )	-10	+20	±0
Rat placenta	-7 3	+14 9	+0 3
Nasal polyp	-5	+14	+4
Bladder carcinoma	-10	+36	+16
Flexner Jobling carcinoma	-7	+31	+17
Rous sarcoma	-5	+30	+20
Retina	-31	+88	+26
Human skin carcinoma	-3 1	+13 8	+7 7
Human mammary carcinoma	-2 6	+11 1	+5 9

tion rate and a high glycolysis under both aerobic and anaerobic conditions (See table 1)

In his general conclusions he has been supported by Rona and Deutsch (168), Murphy (169), and Waterman (170) But Murphy would classify the chorion as a malignant tumor and the spleen as embryonic, and there are even in Warburg's own figures two notable exceptions to the general classification, namely, the gray matter of the brain and the retina, both of which behave as malignant neoplasms

In an effort to eliminate these discrepancies Warburg (171) has resorted to a new value on which to classify tissues. He points out that when the Pasteur reaction functions at its maximum, exactly two molecules of lactic acid are suppressed when one molecule of oxygen is consumed, and on this basis he suggests as a new value "U," which is the aerobic glycolytic rate when the Pasteur reaction is unrestricted by artificial experimental conditions. Of course, this being a somewhat arbitrary and artificial figure, the value may be a negative quantity when the respiratory rate is so great as completely to overbalance the glycolysis.

In this recent paper (171) he gives the accompanying table (table 2), where  $Q_{O_2}$  is the respiratory rate,  $Q_m^{N_2}$  the anaerobic glycolysis, and U the "excess glycolysis."

He further notes in the same article that red blood cells yield positive values for "U" and so they, together with the retina, remain, for the present at least, as exceptions to the general rule.

These probably well established facts have been combated by Bauer and Nyiri, who claim that human carcinoma does not produce any more lactic acid than normal tissue. They find (147) that normal tissue produces from 0 to 1.87 per cent lactic acid per hour, and that carcinoma produces from 0.07 per cent in the cirrhus type to 2.3 per cent in the more cellular types of stomach and breast carcinoma. They further point out that in the figures of Rona and Deutsch (168) three of the human cancers, said to be composed entirely of neoplastic cells, have anaerobic glycolytic rates of but 9.25, 7.9, and 13.25, which are far below those of Warburg for similarly composed animal tumors. They conclude that cancer tissue produces scarcely any more lactic acid aerobically than normal tissue. But Warburg (172) has pointed out that the amount of glycolysis depends, of course, upon the actual number of cancer cells and is, furthermore, very sensitive to changes in the medium. One must, therefore, be cautious in drawing conclusions from human material, in which connective tissue stroma often is far out of proportion to the actual malignant tissue. Rona and Deutsch (168) confirm Warburg as regards human material, though their results, it must be confessed, are lower than his. Furthermore, Warburg and Stahl (173) have shown that the glycolytic rate of a human bladder carcinoma is of the same magnitude as that

of animal tumors Blanchètière (174) also confirms Warburg, though he finds that more glucose disappears than can be accounted for by the lactic acid produced It is further of interest that Cori and others have found, as has been mentioned above (165) (166), that the lactic acid content of the blood is raised by passing through a malignant process, and it would seem, therefore, that the increased glycolytic power of cancer tissue is also found *in vivo* It has been claimed by Waterman (175) that glycolytic power is also shown by cell free extracts of tumor tissue, but his results are not of the same order of magnitude as those of Warburg and for the present it must rest that this rather extraordinary hydrolytic activity is a function of the living cell It has further been asserted by Dische (176) that the non-carcinomatous organs of carcinomatous animals have a higher glycolytic rate than their counterparts from normal animals These observations await confirmation

There is no question but that Warburg's work is upon a firm foundation and it certainly offers a convenient starting point for the study of fundamental carcinomatous processes Yabusoe (177) has indeed shown that certain dyes, as malachite green, crystal violet, cyanin and ethyl violet have a very marked depressant effect on the anaerobic glycolysis of the Flexner-Jobling carcinoma, but there is but little evidence that these dyes *in vivo* have any deterrent action on the growth of cancer

As regards the origin of cancer, Warburg is very conservative He offers as a suggestion that some cells of normal tissue may have all the metabolic activities of neoplastic cells, and that these, under conditions of chronic anoxemia in which the normal cells may be killed, possess sufficient anaerobic glycolytic activity to allow them to develop into a malignant growth

The field of the chemical metabolism of tumors lies open to those investigators who wish to study cancer, and great opportunities are afforded for the advance of the understanding of the fundamental process of growth

#### THE CHEMOTHERAPY OF CANCER

Many chemical substances, chiefly the heavy metals and the dyes, have been tried in the treatment of carcinoma (178) (98) (180)

The Egyptians and Arabians are said (98) to have used arsenic in the treatment of malignant disease, and this substance was employed intermittently throughout the middle ages. As late as 1913, Emil Fisher (181) advocated the use of an organic arsenic compound. More recently Sugiura and Benedict (182) showed that in animals arsenic had a slightly retarding effect on the growth of animal cancers. Iodine, silicon, iron, potassium, and calcium have all been advocated (98), but with none has any degree of success been attained. Sugiura and Benedict (182) have made an exhaustive study of the effects of various salts on the Flexner-Jobling rat carcinoma, and they conclude that copper, arsenic, potassium, and calcium have a slight retarding effect on the tumors, while magnesium accelerates the growth somewhat and tellurium and selenium have no effect on the tumor, though a marked deleterious effect on the animal. Soiland (183) concludes that neither colloidal gold, colloidal copper, nor colloidal lead is of value. Lewin (184) agrees so far as gold is concerned. Gillettee finds (185) selenium too toxic. Wassermann and Keyser (186) advocated for a time a selenium-eosin compound, and Kausch (187) used silver but found it very toxic. Copper, though advocated by several, was finally discarded after an exhaustive study by Weil (188).

Fisher (189) claims beneficial results in animals with exposure to pure oxygen for eighteen hours after the treatment with copper or selenium. Nakahara (190) (191) found increased resistance to transplantable tumors after intraperitoneal injections of unsaturated fatty acids. Numerous dyes have been tried (98) (180), and Roosen (192) has claimed beneficial results with isamin blue, and in this respect Yabusoe's work on the influence of dyes *in vitro* may be recalled (177), but Simpson (193) failed to produce beneficial results with any of 33 coal tar dyes. For a more complete review of all the substances that have been tried in combatting carcinoma, the reader is referred to the monographs of Kammer (98) and Waterman (180).

As long ago as Galen, lead was used in the treatment of carcinoma (98). It was again advocated by Goulard in the eighteenth century (194). It remained for Blair Bell of Liverpool to bring out a lead treatment which has aroused much interest. Bell (195) (196) (197) (199) (200), starting with the theory that the chorion is essentially a malignant tissue (195), attempted to isolate from the foetus (195)

the substance which he believed brought about the cessation of growth of the chorion and consequently normally prevented it from becoming a malignant tumor. This search was unavailing, and he therefore turned his attention to the known abortifacients. He remembered that lead frequently brought about abortion in animals and women, and he determined to try the effect of lead upon carcinomatous tissue. His theory for so doing depends essentially upon his conception of the chorionic epithelium as being fundamentally a malignant tissue, and in favor of this view he brings forward a certain amount of evidence. According to his co-workers (196) (198) (201), the phosphatids of the chorion are very high, as they are also in cancerous tissue. He finds (198) the phosphatid content on the basis of dry weight to be 2.1 for normal tissue, 1.5 for benign tumors, 4.1 for malignant tissues, and 6.8 for the chorion. He further finds that the phosphatid cholesterol ratio is 2.5 for normal tissue, 2.8 for benign tumors, 3.9 for malignant tumors, and 4.7 for chorionic epithelium. Again he maintains that the chorionic epithelium shows by Warburg's classification a metabolism characteristic of a malignant tissue, and some support here is rendered by Murphy (169). But Warburg (202) has recently shown unequivocally that the chorion behaves like an embryonic rather than a neoplastic tissue. Bell also believes cancer to be very rare in individuals suffering from lead poisoning (198), but his figures in this respect have been vigorously combatted by the Medical Research Council (203). He points out that lead is toxic to many normal tissues (brain, gonads, blood) and especially so to actively growing tissues. He finds, for instance, that lead salts in small concentration will kill hyacinth bulbs, and that concentrations of 1 to 100,000 will prevent the germination of frogs' eggs, whereas the adult frog can stand concentrations of 1 to 1000 (195). Assuming, as he does, that "the primary metabolic factors associated with neoplasia are the same in both types (innocent and malignant)—indeed in all types of growth," he builds up a logical basis for the "treatment of every malignant growth with preparations" of lead. It may be objected that some of his facts need substantiation and that a substance toxic for normal adult tissue in relatively small amounts is not ideal as a chemotherapeutic agent against neoplastic disease on account of the almost certain narrow margin of safety. He claims,

however (195), that lead concentrates in the cancerous tissue to a greater extent than in other tissues, except the testis. In this respect, Waterman (180) (204) does not agree, as he finds more lead in the normal tissues than in the cancer. Martland (205) found no histological evidence of the presence of lead in his human cases, nor did he find, on chemical analysis, that the lead was in greater amounts in the tumor. The theory, however, is less important than the clinical facts.

Bell originally used inorganic and organic lead compounds, but finally came to employ colloidal lead. This was prepared (195) (197) by Bredig's sparking method in an aqueous solution (0.4 per cent) of gelatin and 0.027 per cent calcium chloride. The final solution, as used, contained 0.5 per cent lead and is not stable, except for short periods of time. This colloidal solution was injected intravenously in doses of about 50 to 100 mgm. over a period of weeks. He advocates the removal, surgically, of as much of the tumor as possible, and cautions against the use of lead in tumors of the lung or brain, in obstructive jaundice, and in cases where the blood is anemic or when chronic nephritis, even of a slight grade, is present. His last published figures are as follows (197):

Admitted but died before treatment could be started	20
Died before treatment could be completed	50
Died of intercurrent affections	3
Died after treatment	106
Too recent for results to be estimated	14
Died as a result of extensive destruction of the tumor by lead	4
Complete treatment refused but patients leading normal lives	9
Disease completely arrested	10
Believed cured	31

As regards the direct effect of lead on the tumor, there is some difference of opinion. Glynn (206) found no histological changes. Fry (207), likewise, found no evidence suggesting the destruction of the tumor by lead, though he did find that the kidneys showed extensive tubular degeneration. Wood (178) (208), however, noted in animals marked necrosis of the neoplastic tissue and thrombosis of the vessels supplying the tumor, and others have noted apparent massive necrosis of human tumors (209). From a chemical and metabolic point of view it has been shown (125) that lead, instead of decreasing, actually increases the anaerobic glycolysis of tumor tissue,

while copper and zinc were shown to decrease it 17 and 33 per cent respectively

It is difficult to evaluate correctly Bell's figures, because in his published reports details are scant indeed. No doubt some cases have been benefited, how many, it is impossible at this time to say. Other authors fail, however, to get such promising results as Blair Bell. Ullman (209) (210) found that when using colloid metallic lead his patients nearly constantly suffered from lumbar pain, hematuria and acute nephritis, and that the hemoglobin fall was marked and rapid. For these and other reasons, he changed to a colloidal lead phosphate—a very logical change in view of the fate of lead when injected into the body—and found that this compound was much less toxic to the organism as a whole. Ullman (209) (210) now advocates the lead phosphate and reports favorably on its use. Martland (205), preparing his colloidal metal in a different manner, reports that in 15 cases there was only a temporary improvement, and he feels that no effect is produced on the tumor unless thrombosis is brought about. Wood (178), on the contrary, says, "For the first time a substance has been found that will arrest the growth of carcinoma for a period of from one to five years, and this in patients both inoperable and beyond the power of irradiation to effect a cure." Stone and Carver (211) review the subject very completely and report their own results from the Memorial Hospital, New York. Their lead colloid was prepared most carefully by a modified Bredig's method and was stable over a considerable period of time. They found no serious immediate symptoms or serious after effects except anemia, and from this the patient rapidly recovered when lead was temporarily omitted. They saw appreciable regressions in four out of seven mammary cancers and in two a "temporary cure." There seemed, also, to be some benefit in three cases of osteogenetic sarcoma and one case of Ewing's tumor. It is interesting in view of Bell's original theory to note that the treatment failed completely in the case of a chorioepithelioma of the vagina. They conclude that lead does not offer a general cure for malignant neoplasms, but that in mammary cancer and osteogenetic sarcoma it may—either alone or with x-ray—be of value. Wood (212), working with rat tumors, finds evidence that lead increases the sensitivity of the tumors to x ray and advo-



cates a combined treatment Ullmann (200) joins in this recommendation.

It is probably still too early to say whether or not lead will take a permanent place in the therapy of cancer More work will have to be done in a very carefully controlled manner and several years will elapse before the true value of the substance is known It can be said, however, that at the present writing it is not a treatment to be attempted outside of a fully equipped and well organized research hospital under the charge of both expert clinicians and expert chemists

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# PLEURAL AND PULMONARY<sup>or 4</sup> LESIONS IN RHEUMATIC FEVER

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## INTRODUCTION

For almost a century the main interest of the student of rheumatic fever has been centered upon the cardiac lesion, and justly so, for, as Lasègue has aptly said rheumatic fever is a disease which "licks the joints, the pleura and meninges but bites the heart" (1) Unquestionably the most serious clinical manifestations of the disease are cardiac in nature and furthermore the discovery by Aschoff in 1904, of specific rheumatic lesions in the myocardium has magnified the importance of the heart in this disease. And yet by focusing our attention too closely upon a single organ or upon lesions in that organ, our conception of the pathogenesis of this condition may become one-sided, for after all, we realize quite fully that rheumatic fever is a generalized process of which the joint and cardiac lesions are merely local manifestations. From a pathological standpoint an appreciation of the generalized nature of this process has perhaps found expression in the work of Mosler (2), and others before him, who have believed that rheumatic fever has a selective action upon serous membranes with which the heart happens to be heavily endowed. Pappenheimer and Von Glahn (3) also have recently stressed the generalized nature of this disease in emphasizing the presence of specific rheumatic lesions in peripheral blood vessels and have called attention to "the fact that the pathology of rheumatic infection does not begin and end with the Aschoff nodule."

The present review will deal with the lesions involving the respiratory tract which occur in rheumatic fever. These also have received their share of attention in the past, pleurisy and pneumonia are said to represent complications of the disease which occur next in frequency to the

cardiac lesions and they are discussed in almost every text book article on rheumatic fever. Nevertheless, they are still somewhat ill-defined due possibly to the fact that although there have been innumerable clinical speculations as to the nature of the pulmonary disturbances which may be present, the lungs in active rheumatic fever do not seem to have been subjected to any very extensive pathological study. This article is concerned therefore with the history of these rheumatic pulmonary lesions together with a review of some of the current clinical conceptions as to their nature, compared with some of the pathological findings which have been observed in the active stages of the disease.

#### HISTORICAL

The early history of rheumatic fever has been reviewed in a number of well known articles on the subject (4) (5) (6) (7), to which the reader may be referred. Furthermore the early recognition and development of our knowledge with regard to rheumatic heart disease has also been reviewed in Coombs' treatise (8), and in a recent excellent article by Sacks (9). Lebreton (10), and Bezançon and Weil (11) have both traced the beginnings of our knowledge of the pleural lesions but, apart from these last authors, the history of pulmonary lesions in rheumatic fever has received only passing attention, in spite of the fact that, although they were not defined, their existence was hinted at many years prior to the discovery of the cardiac lesion. It may, however, be giving undue credit to the early observers, to assert that they appreciated the nature of the pulmonary lesions for evidently many of the symptoms such as cough and dyspnea, thought originally to be due to disease of the lungs per se, were actually pulmonary manifestations of a cardiac lesion, but at least the fact that in rheumatic fever fluid might accumulate in the pleural cavities and that the lungs might be correspondingly compressed was recognized many years prior to the recognition of the cardiac lesion.

The story of the early recognition of rheumatic fever as a disease entity and the growth of the idea that it injured the thoracic viscera in some manner seems to be of sufficient interest to warrant a brief review. It may be well to point out at the outset that the term rheumatism has always been more or less of an indefinite one, partly because

it already had a wide usage before it came to be applied to rheumatic fever and partly because rheumatic fever is not a disease which can be readily and easily defined. In fact the confusion which still exists in our generation with regard to the use of this term is perhaps sufficient to explain the difficulties which beset the earliest attempts to define rheumatic fever or acute rheumatism as a disease entity and to differentiate it from the hosts of conditions which it may simulate. Primarily the attempt will not be made to sift through the earliest literature, i.e., prior to the seventeenth century, although we do find isolated descriptions of polyarthritis dating back to the time of Hippocrates. In fact Hippocrates' description, which is quoted from Chomel (12), of a type of arthritis which travels rapidly from joint to joint, might be very logically interpreted as referring to manifestations of rheumatic fever but the syndrome was not given a name until centuries later it had the misfortune to be called rheumatism.

It is well known that the term "rheumatism" was derived from a much older term *ῥεῖμα* meaning a fluxion. We frequently read in early writings of a "rheum," signifying a certain type of catarrh which flowed from the brain into various regions of the body and caused pain and distress wherever it lodged but it is a little difficult to see at first how the term "rheumatism," meaning, to be afflicted with defluxions, came to be applied to the disease which now bears its name. A probable explanation which has been suggested, is that the rapidity with which the symptoms traveled from one joint to another suggested that the disease flowed about the body.

To Guillaume Baillou or Billonius, a physician of Paris (1538-1616), is attributed the first use of the term rheumatism to describe acute polyarthritis (13). This author had in his early writings used the term *rheumatismus* in the sense of Galen's so called "rheumatic indisposition" by which he implied a certain weakness due to the loss of fluid from the body including blood or pus, but in Baillou's famous treatise entitled *De Rheumatismo et Pleuritide Dorsale*, he employed the term *ῥευματισμὸς* to describe a disease characterized by fever and polyarthritis which he believed could be differentiated from arthritis and gout. He says: "And although arthritis occurs in a single part this disease is that 'rheumatismus' which involves the whole body



with pain, tension and a keen sense of heat. <sup>1</sup> He justified his application of the term rheumatism to this condition by stating that defluxions did not always start from the head, but there were also defluxions which could occur from the viscera to the external parts as was apparently the case in this disease. He did not believe that the joint symptoms and the fever were the only manifestations of the disease, for he refers, in a vague sort of manner to be sure, to an involvement of the head, lungs, spleen and liver, and to "a disturbance and a corruption of the blood." In that era, however, when the humoral theories of disease were in fashion it was probably quite natural to conceive of a condition such as Baillou's *rheumatismus*, as a generalized process which could readily circulate throughout the body and so we are hesitant to believe that our worthy author really had any clear cut conception of the damage which his disease inflicted upon the internal organs. This treatise was first published in 1635, nineteen years after the author's death. With it appeared an article on pleurisy, but there is no suggestion that he had considered the existence of a relationship between the two.

However, the best of the earliest descriptions of rheumatic fever was that of Sydenham, published in 1676 (14), forty years after the appearance of the treatise by Baillou. Sydenham's ability to single out this disease and differentiate it from the host of conditions which it simulates may be attributed in some measure to the fact that he also recognized gout as a definite entity (15), quite distinct from rheumatic fever. Some intimation of his views on the subject may be gained from the following extract which has been taken from Latham's translation of the article on rheumatism in the *Observationes Medicae* (16)

"This disease, when separate from the fever, is often called arthritis (gout). Nevertheless, it differs essentially from that disease, as every one knows who knows the two diseases well. This confusion may perhaps explain why it is that medical writers have passed so lightly over rheumatism, unless, indeed, we choose to suppose that the long list of human ailments has lately been increased by a fresh addition."

<sup>1</sup> Et quod arthritis est in parte aliqua, idipsum est iste *ῥευματισμός* in toto corpore, dolore, tensione & caloris acriusculi sensione

Whether Sydenham believed that the disease manifested itself only in the form of fever and joint symptoms, or whether he had any inkling of the frequently associated grave internal manifestations is a point which we have attempted to analyze. It seems justifiable to assume that he was aware that the joint symptoms alone did not tell the whole story but he was probably so anxious to identify the condition as a definite and distinct clinical entity, recognizable on the basis of polyarthritis that he has perhaps avoided, as far as possible, any statements with regard to vague and ill defined internal lesions which might serve to obscure the picture. However, he surmounted his difficulties with a compromise by creating a special subdivision of the disease which he designated as "scorbutic rheumatism," admitting in honest fashion that the term "scorbutic" was in some measure a subterfuge. As an explanation of the use of this term, he says

"That scurvy is rife and common in the northern countries, I admit, that it is so common as is generally believed, I doubt. Many of the cases of the so-called scurvy are cases of disease in the process of formation, many of disease imperfectly subdued.

"This applies to incipient dropsy as well as to departing gout. The saving of the vulgar is as follows: *When scurvy ends, dropsy begins*. Now this only means that when dropsy has fairly shown itself by clear signs, the preconceived notion of a scurvy falls to the ground.

"Now, however great may be the difference between true rheumatism and true scurvy, there is a sort of the former disease which cannot be denied to approach the latter, both in respect to its symptoms and its cure, and this I shall call scorbutic rheumatism. The pains come sometimes in one part sometimes in another, they seldom occasion much suffering, seldom are attended with fevers. They are less fixed to one spot, are more erratic, and more uncertain, their accompanying symptoms being anomalous, and disorderly also. At times it afflicts this or that joint, at times the inward parts only."

Various interpretations may be put upon the above statements, certainly we cannot say that Sydenham appreciated the existence of the cardiac lesion but we cannot fail to note his appreciation of the fact that "inward parts" were affected and, to remark upon his timely insertion of what was at that time apparently a popular phrase, viz "*When scurvy ends, dropsy begins*." The difficulties which confront

the internist of today in his efforts to diagnose rheumatic fever in the absence of joint symptoms bear witness to the accuracy of Sydenham's observations that under certain circumstances the disease is apt to be called by any name which happens to be the fashion

Fifty years later we find Boerhaave referring to Sydenham's description as the best that he can find of Rheumatic Fever or Rheumatism, as it has been called since the time of Baillou. Boerhaave included a section on Rheumatism in the fifth or last edition of his famous Aphorisms which appeared in 1737 (17). In it he adds little to Sydenham's description but he makes the very definite statement that besides the joint symptoms, the disease invades "sometimes the brain, lungs and bowels."

By the middle of the eighteenth century acute rheumatism must have been fairly widely recognized. Subsequent authors (18) (19) succeeded in amplifying the disease picture with considerable vigor for it was becoming apparent that the condition was more common than was originally suspected, and not the least of its peculiarities lay in its ability to give rise to "metastases" from the joints to the internal organs.

Storck laid great stress on this point and frequently refers to the "partly fixed and partly wandering" nature of the pain so that it "seizes the external, and at another time the internal parts." Furthermore we can detect the first definite intimation of the presence of the signs and symptoms of cardiac disease in the following statements: "then the breast was oppressed, and the patients began to cough," and again it "forms lymphatic tumors, which appear on the external superficies of the body, and upon being lanced, void a yellow viscid serum, that may be inspissated by gentle heat. Tumors may be collected in the interior parts" as, "the dissection of people who died in this malady has well evinced." To corroborate these statements Storck has described the necropsy findings in three of his patients, as follows:

"Three patients whose interior parts were seized by this serum, which had been dispersed over the whole superficies of the body died of rheumatism. In two of the bodies, a large quantity of yellow, gluey matter was found between the membranes surrounding the lungs, and the lungs them-

selves, and the whole substance of the lungs was compressed into a very small space

"In the third patient, the tumor of the limbs subsided, and a difficult respiration followed, with a convulsive cough, which yielded to no remedies, so that the poor man being exhausted of his strength, died within fourteen days. In the middle of the right lung, a sac was found which contained 5 pounds of acrid yellow serum. The other parts were sound" (19)

The description of these necropsies are the earliest which we have been able to find describing the thoracic viscera in cases of rheumatism.

Lettsom made a similar observation, although several years later (1787), in reporting upon the necropsy findings from a fatal case of acute rheumatism in a child of six (20), and in that instance was greatly impressed by the accumulation of fluid in the chest and pericardial cavities. The lesions which these early observers have described are indeed comparable to those encountered in cases of cardiac decompensation associated with rheumatic carditis, in at least two of which, general anasarca seems to have been present. In none of them however, can we assume from the description that the observer was really aware of the presence of a cardiac lesion. However, with the increasing frequency with which necropsies were beginning to be performed it was evident that the cardiac lesion could not long remain unnoticed and in fact it was only a year after the publication of Lettsom's case that David Pitcairn is said to have first recognized its existence. Pitcairn's observations were made in 1788 while he was, physician to St. Bartholomew's Hospital in London, and a year afterward Edward Jenner also recognized, apparently quite independently, the presence of heart disease following acute rheumatism.

We will not pursue further the story of the development of our knowledge of rheumatic heart disease for it has been amply reviewed by Sacks in a recent article to which the reader is referred (9), but will rather concern ourselves for the moment with the developing conceptions of pleural and pulmonary lesions. The Viennese physician Maximilian Stoll (1742-1787) was apparently quite impressed by the accumulation of fluid in the pleural cavity in association with cardiac disease and he is said to have been the first to speak of "rheumatic pleurisy" and "rheumatic peripneumonia" which he listed as one of three types of pneumonia (21) (22). However, he failed to dwell on

the nature of the pleural or pulmonary lesions, or to furnish us with any pathological descriptions so that subsequent French writers were not inclined to put much reliance in his observations, made as they were, before the days of accurate physical diagnostic methods. Nevertheless it is quite evident that Stoll was aware of the presence of a disorder involving the pleura and lungs which occurred during the course of acute rheumatism.

It is to the French school that we owe the early development of our conception of the pleural lesions. The best known of the earliest treatises is the "Essai sur le Rhumatisme" by Chomel (23), published in 1813 at a time when he and Louis were fellow pupils in Paris. He mentions pulmonary rheumatism but speaks with caution of the relationship which the lesions in the lungs bore to disease of the joints, saying "Once we considered inflammation of the pleura or lung which follows rheumatism and seems to cease on its return as rheumatismal but today we regard them as different affections."

In spite of the caution with which Chomel treated the subject of rheumatic pleurisy it soon became accepted as one of the manifestations of the disease and is freely discussed as such by Boulland (24), and Grisolles (25). Grisolles stated that inflammation of the pleura which was associated with the cardiac lesion was quite common although pneumonia on the contrary was very rare.

Following closely upon the heels of these French observations came a series of English studies which found expression in the Lectures of Peter Latham, published in 1845 (26) and in Fuller's *Treatise on Rheumatism*, 1854 (27). These authors went several steps beyond the cautious viewpoint of the French with regard to the extent of the pulmonary lesions in rheumatism, and definitely championed the concept of Rheumatic Pneumonia as part of the general disease picture. We should emphasize, however, that Dr Latham's impressions about the lungs, which have been widely quoted, were based essentially upon clinical observations and the lesions which he listed represented his interpretation of clinical signs rather than an intimate knowledge of the lesions themselves. In speaking of the pulmonary complications he says. "Such forms of pulmonary inflammation are portentous ingredients in the clinical history of acute rheumatism, and give a fearful interest to it." He laid great stress upon the frequency with

which the lungs are involved, "in all the several structures of which they are composed," stating that the diseases which result are bronchitis, pneumonia and pleurisy. The incidence of these conditions in his series of 136 cases is given as follows: the heart was inflamed in 90 and the lungs in 24 or (17 per cent), of which 4 were bronchitis 18 pneumonia and 2 pleurisy. As will be shown later this is a very low figure for the incidence of pleurisy but the author admits that pneumonia may have "veiled the presence of pleurisy" (26).

Fuller (27) also pointed out the frequency with which inflammation of the lungs and pleura occurred, particularly in those cases where the pericardium was involved, although he did not believe that the disease spread to the pleura by contiguity. In his series of 246 cases of acute rheumatism, pulmonary lesions are recorded in 41, bronchitis was noted in 13 instances, pneumonia in 26, and pleurisy in 13. However, these percentages were also based upon clinical observations and the high incidence of pneumonia is not shown by the findings in Fuller's series of 16 necropsies which appears in the same treatise. In the necropsied cases, pneumonia is recorded twice, pleurisy five times and bronchitis once. Something of a discrepancy between these figures and the clinical ones is at once apparent.

Latham's and Fuller's statistics have now been published for more than seventy five years and it seems hardly necessary to devote quite so much space and time to them when we consider that more accurate statistics are now available, were it not for the fact that they have been so widely quoted in the literature as standard figures on the incidence of "rheumatic pneumonia." The contribution which these authors made to this subject was very appreciable although it was essentially that of calling attention to the prevalence and the importance of pulmonary involvement in rheumatic fever rather than to specifying the exact nature of these conditions and the frequency of their occurrence. An analysis of their results shows that the main claims which they made were, not that pleurisy was present in 16 to 19 per cent of the cases, or that pneumonia was present in 10 to 12 per cent, but rather that they found physical signs in the chest pointing to pleurisy or pneumonia in the above percentages.

Apparently it was not long before the discrepancy between the clinical and pathological findings with regard to the incidence of lobar

pneumonia in acute rheumatism was detected and Ormerod (1858) (28) in discussing the pulmonary lesions in rheumatism says

"On carefully looking over the records of dissection, the descriptions of the morbid appearances do not seem, on the whole, to represent the same results of pneumonia as would probably have been found in as many simple cases of this nature. The terms congestion and softening and the equivocal expression splenisation (collapse) occurs more frequently than the explicit mention of red or grey hepatization."

The same skeptical viewpoint was taken by Vulpian (29) who says that the lesion spoken of as pneumonia appears to be a splenisation or "perhaps a simple collapse," and later by Sée (30), who believed rheumatic pneumonia to be very rare. Nevertheless the firmly rooted concept that rheumatic pneumonia was a common manifestation of the disease was not to be dropped lightly as is evidenced by the discussion which appeared spasmodically during the years of 1860-1885 in English and French literature (31) (32) (33). The German school, however, were not impressed with the idea that pneumonia was a prominent manifestation of acute rheumatism and in Lebert's excellent monograph written in 1860 (34) he states with considerable firmness that pneumonia in rheumatism is rare, giving an incidence of 1.4 per cent in his clinical series of 140 cases. He recognized on the other hand, the frequency of rheumatic pleurisy and gives an accurate description of it.

Our present conception of these lesions will be given in a subsequent section of this article and so we will not pursue their historical aspects further. One other concept, however, seems to be worth considering in that it touches upon the problem of rheumatic pleurisy. This is the development of the idea that rheumatic fever is a disease of the serous membranes essentially involving the synovial membranes, the pericardium and the pleura. The idea is by no means a recent one, for more than a century ago observers noted the similarity between the tissues which are affected in this disease. Early in the nineteenth century (1816) this thought had found expression in Balfour's Observations (35). He says

"That in acute Rheumatism a phlogistic diathesis of the system prevails, admits not of doubt, and that there is an affection of either the muscular fiber, or of the cellular membrane, or of both, is equally certain

"The cellular membrane abounds everywhere in the body . All the blood vessels receive a coat from it, from the Aorta, where it emerges from the heart, to the minutest capillary that enters a tendon "

Tuller in 1854 (27) also speaks of this idea as follows

"But not only does the rheumatic virus obey the general law of poisons, in that its action is not limited to any one texture or organ of the body it further resembles this class of agents in displaying a partiality for a particular texture and particular organs upon which it fixes in preference to others. Such a texture is the white fibrous tissue, which enters into the formation of the aponeurotic sheaths, the fasciae, the capsules of the joints, the ligaments and tendons, the fibro serous membranes in various parts of the body. The parts, therefore most commonly affected, are the joints and their surrounding structures, the valvular apparatus of the heart, and the fibrous serous covering of the heart, the strong white glistening sac of the pericardium "

Fifty years later Mosler (2) emphasized this same concept in the use of the term "Polyserositis rheumatica," adding the meninges and the peritoneum to the list of serous membranes which had already been mentioned

#### RHEUMATIC PLEURISY

It is generally recognized today that next to cardiac involvement pleurisy is the most common complication of rheumatic fever (36). In fact, as is also the case with the carditis, it is questionable whether pleurisy should be regarded as a complication rather than another manifestation of rheumatic disease of the serous membranes of which pericarditis, pleurisy and even peritonitis are examples (2)

By the above use of the term pleurisy, a somewhat indefinite term to say the least, we mean rheumatic pleurisy, a specific type of pleural involvement which may be as characteristically rheumatic as the pericardial lesion. This fact has not, however, been always appreciated and is probably responsible for differences of opinion, for, of course, one cannot discuss pleurisy as a specific lesion of rheumatic fever unless we can at the same time eliminate other sources of pleural infection such as might result from an intercurrent bronchopneumonia and can also define just what we mean by pleurisy, being careful to differentiate pleural exudates from pleural transudates. The occa-



sional difficulty which confronts the pathologist at the autopsy table in determining the actual presence of an inflammation of the pleura is sufficient to emphasize the difficulties which beset the clinician. From the clinical standpoint the presence of pleural friction rubs accompanied by appropriate signs and symptoms may perhaps be accepted as useful criteria for determining the presence of a certain type or stage of inflammation of the pleura and it has been upon the interpretation of such signs as these that most of the statistics have been compiled. However, the variables which enter the problem of making a clinical diagnosis of pleurisy are very appreciable. When a pleural exudate becomes partially or wholly organized our ability to detect it by means of physical signs is seriously impaired. If an effusion develops it probably cannot be detected until it has reached a certain size and furthermore the mere presence of fluid in the pleural cavities as shown by auscultation and percussion or by roentgenograms of the chest is again insufficient evidence upon which to base the diagnosis of pleurisy, particularly in rheumatic fever, for the frequent presence of transudates associated with a failing circulation may leave us in doubt as to the nature of the fluid present. These factors are in some measure responsible for the discrepancies which exist among clinical statistics on the incidence of pleurisy in rheumatic fever which have been listed by various authors, as follows: Lebert—10 per cent, 1860 (34), Garrod—15 per cent, 1890 (4), Pribram—3 per cent, 1899 (6), Mosler—14.7 per cent, 1910 (2), Rolly—2.4 per cent, 1920 (37), Swift—5 to 10 per cent, 1927 (38).

Nevertheless in spite of the difficulties of diagnosis, the clinical picture of rheumatic pleurisy can be defined. It seems to occur either in association with polyarthritis or as an independent feature of the disease. According to Swift (36) it generally indicates a severe rheumatic infection, but occasionally is the chief evidence of a relapse in a patient who has had joint involvement weeks or months before. Rarely it is the initial manifestation of rheumatic fever, although probably certain cases of so-called idiopathic pleurisy are rheumatic in origin. It is often heralded by an intensification of the signs of general infection and in its early stages by the characteristic sharp, stabbing pain on inspiration, by rapid and shallow breathing, friction rubs and other classical physical signs of the presence of a fibrinous exudate on

the pleural surface These signs may persist for several days or even weeks but, as a rule, the so called dry pleurisy is followed within twenty-four to forty-eight hours by the accumulation of fluid in the pleural cavity which may persist for varying periods of time In the absence of fluid the acute pleural inflammation is followed by organization of the fibrinous exudate and adhesions between the visceral and parietal pleura Induration and thickening of the pleura similar to the findings noted in tuberculosis of the pleura have apparently not been observed—Rolly (37)

Fibrinous pleurisy or what might be termed "dry pleurisy" is not a frequent finding at necropsy, but the commonest manifestation is that of pleurisy with effusion This we have encountered in more than half of the active fatal cases which we have studied As we have already stated, the factors which contribute to the accumulation of fluid in the pleural cavity in rheumatic fever are multiple but our studies have convinced us that inflammation of the pleura plays a leading rôle in this process, for the amount of fluid exudate and its character, seems to be closely related to the degree of pleural involvement In general the pleural inflammation resembles that of the pericardium The usual picture at necropsy is to find the lungs moderately compressed particularly in their dependent portions and over these areas the pleura appears slightly opaque Closer inspection often reveals the presence of a fine, thin film of fibrin on the surface, or, as the process advances in extent, and particularly in those cases in which the amount of fluid in each pleural cavity exceeds a liter we may find the presence of a thick, fibrinous exudate on both parietal and visceral pleura Subsequently, organization of the fibrinous adhesions occurs and this process may be encountered in all stages A common finding is that of an obliterative pleurisy associated with the combination of loose fibrous and fibrinous tissue giving rise to fairly soft, white adhesions which often enclose loculated areas of fluid As with many inflammations of the pleura eventual disappearance of the exudate occurs and old fibrous adhesions are left as landmarks of the previous lesion We have not encountered, however, a really thickened hyalinized pleura analogous to the picture seen so frequently in the older stages of tuberculous pleurisy

Histologically the appearance of this lesion again recalls the picture

of rheumatic pericarditis. It is characterized primarily by changes in the pleural endothelium causing metaplasia and eventual death and desquamation of the endothelial cells. This is accompanied by a characteristic type of severe, chronic, non-suppurative inflammatory reaction throughout the subpleural layers. Subsequently we have evidences of healing, but the process of repair is indeed a slow one.

Unfortunately this picture is not sufficiently illuminating to tell us the nature of the rheumatic lesion of the pleura, although it evidently is an example of the selective manner in which this disease manifests itself upon serous surfaces. We still do not know whether this process is a lesion of the pleura per se, starting primarily in the endothelial lining cells or whether it is a surface manifestation of a deep seated although less prominent pulmonary lesion. Besançon and Weil (11) in employing the term "cortico-pleurite" in rheumatic pleurisy have endeavored to emphasize that the pleura and subpleural layers are involved.

Furthermore we do not know whether the pleural lesion represents an extension from the pericardial lesion or is an independent lesion. There seems to be little doubt, however, that rheumatic pleurisy bears some relationship to the cardiac lesion and many authors have called attention to the high incidence of pleural involvement associated with pericarditis. Rolly's figures on the clinical incidence of pleurisy and pericarditis are interesting in this respect. From a series of 3620 cases of acute rheumatic fever, disease of the serous membranes was noted in 140 cases or 3.9 per cent. Pericarditis was present in 115 or 3.2 per cent. Pleurisy was present in 88 or 2.5 per cent, whereas both pericardium and pleura were involved in 44 instances (37). Furthermore, although the condition is often bilateral, rheumatic pleurisy has been said to occur more frequently on the left side than on the right due probably to the proximity of the pericardium. Rolly observed 32 instances of pleurisy on the left side as opposed to 16 on the right. However, Lange, quoted by Garrod (4), noted in a series of 125 cases of pleurisy occurring in rheumatic fever, that it was bilateral in 60, unilateral on the right side in 49 cases, and on the left in 16. The more frequent occurrence of pleurisy with effusion on the right side as opposed to the left has been our experience. It has been said that pleurisy may develop without carditis but this is hard to

prove. However, in a series of thirty necropsied cases in all of which death occurred during the active stage of rheumatic fever, we have recently observed four instances of active fibrinous pleurisy occurring in the absence of an active pericarditis. It is evident none the less that the pericardial and pleural lesions are closely related by virtue of their proximity and by virtue of the fact that they appear in the same general type of tissue, but from the data at hand we feel that the paths of infection through which the pleura becomes involved cannot be satisfactorily traced, particularly as we do not know the nature of the infection with which we have to deal. In any event, our recent knowledge of the widespread distribution of rheumatic vascular lesions throughout the body involving the peripheral arteries and arterioles, makes it easier to conceive of the pleural lesions as part of a generalized process without postulating that the disease must have spread by direct extension from the pericardium.

*Pleural fluid* The accumulation of fluid in the pleural cavity is almost constantly associated with rheumatic pleurisy. Associated with its presence we have, of course, varying degrees of pulmonary compression which exert a very definite influence upon cardio respiratory function. These effusions accumulate quickly and are said to be absorbed or to disappear relatively quickly. From a purely therapeutic standpoint they seldom require aspiration.

The factors which contribute to the accumulation of fluid or exudate in the pleural cavity in rheumatic fever are evidently multiple and as a result, the character of the fluid may present very wide differences. Paramount among them is the extent and activity of the rheumatic inflammatory lesion of the pleura. In some instances this inflammation may be supplemented by mechanical irritation of the pleural surfaces, as the result of an enormously enlarged pericardial sac. Among other factors, the presence of generalized edema associated with cardiac insufficiency of course exerts a profound influence upon the amount as well as the character of the fluid. The presence of pulmonary infarcts which are not uncommon in rheumatic carditis may play a rôle in this process and finally a superimposed or intercurrent pulmonary infection may well exert an effect upon the accumulation and character of the pleural exudate. This multiplicity of etiological factors makes it imperative that we should be more or less

familiar with the state of affairs within the thorax before attempting to study this fluid

The typically rheumatic sero-fibrinous pleural exudate appears as clear or slightly turbid, straw colored fluid and within an hour after withdrawal, a dense coagulum usually forms in which cells are enmeshed, leaving a clear, serous fluid. One is perhaps more impressed with gross evidences of the fibrin content of this fluid at the necropsy table than at the bed side for a glance at the open chest will reveal the presence of small flecks or strings, or in some instances huge masses, which may be either floating or deposited upon pleural surfaces. As most of these masses are too large to penetrate the lumen of the ordinary trocar they do not appear in the usual specimen obtained by aspiration.

In young children we have noted on several occasions the presence of an hemorrhagic effusion in the pleural as well as the pericardial cavities.

Our knowledge of the chemical constituents of these pleural exudates is relatively slight. Bezançon and Weil state that they are rich in albumin and that they give a positive Rivalta reaction<sup>2</sup>. They record a series of determinations on the amounts of fibrin which have been found in samples of rheumatic pleural fluid as compared with others which have been found in effusions of tuberculous origin and transudates which have occurred in cases of cardiac decompensation. Their figures show that there is a slight similarity of fibrin content, between the effusions from the first two types of cases in this series. At the same time the authors emphasize the fact that their results give a very inaccurate conception of the total amounts of fibrin present for the figures only represent the fibrinogen which is in solution without giving any conception of the amount of fibrin which may have been precipitated upon the pleural surfaces.

We know comparatively little with regard to the physical chemistry of these fluids, the types of proteins which they contain, their non-protein elements or electrolyte content.

Microscopic examination of a film of the sediment from such an effu-

<sup>2</sup> The Rivalta reaction has been used as a test for distinguishing between exudates and transudates, a positive result signifying the former. For a brief review of the literature on the subject the reader is referred to Wells' Text Book of Chemical Pathology (39).

sion shows moderate numbers of polymorphonuclear cells, some lymphocytes and desquamated endothelial cells from the pleura Ravaut (40), Bezanson and Weil (11) and other French authors have laid great stress upon the presence of endothelial cells in this type of fluid "La cellule endothéliale est l'élément caractéristique de la pleurésie rhumatismale" These are found as single cells or in sheets and their relative incidence is said to vary for they may be greatly outnumbered by neutrophile polynuclears or lymphocytes during acute or subacute stages of the lesion Sabrazes (41) has studied these fluctuations which may be observed in the differential counts of the cells in the pleural fluid at different stages of the disease

Innumerable bacteriological studies have been made on the pleural exudates in rheumatic fever These have been reviewed by Singer (42), Pribram (6), and Rolly (37) The great majority have yielded negative results Occasionally organisms, representing for the most part different types, have been isolated but the findings do not lend themselves to ready interpretation In our own experience we have repeatedly failed to demonstrate or isolate bacteria from this fluid

#### VASCULAR LESIONS

Besides the pleural involvement another specific pulmonary manifestation of rheumatic fever occurs in the form of slight changes in and about the vessel walls These lesions have proved to be of such importance in the lung that a brief review of their general history seems warranted

Accurate histological descriptions of the vascular lesions in rheumatic fever represent a comparatively recent contribution, although for many years clinical and gross pathological observations on so called rheumatic aortitis have been prominent particularly in French medical literature<sup>1</sup> The first histological descriptions of these lesions have been attributed to Klotz who reported his studies in 1912 (43) A few years previously, however, (1909) Coombs (44) had noted the presence of lesions in the adventitial layers of the ascending portion of the aorta and remarked upon their similarity to the specific lesion or Aschoff bodies of the myocardium Coombs was of the opinion that

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We know comparatively little with regard to the physical chemistry of these fluids, the types of proteins which they contain, their non-protein elements or electrolyte content.

Microscopic examination of a film of the sediment from such an effu-

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sion shows moderate numbers of polymorphonuclear cells, some lymphocytes and desquamated endothelial cells from the pleura. Ravaut (40), Bezangon and Weil (11) and other French authors have laid great stress upon the presence of endothelial cells in this type of fluid. "*La cellule endothéliale est l'élément caractéristique de la pleurésie rhumatismale.*" These are found as single cells or in sheets and their relative incidence is said to vary for they may be greatly outnumbered by neutrophile polynuclears or lymphocytes during acute or subacute stages of the lesion. Sabrazes (41) has studied these fluctuations which may be observed in the differential counts of the cells in the pleural fluid at different stages of the disease.

Innumerable bacteriological studies have been made on the pleural exudates in rheumatic fever. These have been reviewed by Singer (42), Pribram (6) and Rolly (37). The great majority have yielded negative results. Occasionally organisms, representing for the most part different types, have been isolated but the findings do not lend themselves to ready interpretation. In our own experience we have repeatedly failed to demonstrate or isolate bacteria from this fluid.

#### VASCULAR LESIONS

Besides the pleural involvement another specific pulmonary manifestation of rheumatic fever occurs in the form of slight changes in and about the vessel walls. These lesions have proved to be of such importance in the lung that a brief review of their general history seems warranted.

Accurate histological descriptions of the vascular lesions in rheumatic fever represent a comparatively recent contribution although for many years clinical and gross pathological observations on so-called rheumatic aortitis have been prominent particularly in French medical literature.<sup>1</sup> The first histological descriptions of these lesions have been attributed to Klotz who reported his studies in 1912 (43). A few years previously, however (1909) Coombs (44) had noted the presence of lesions in the adventitial layers of the ascending portion of the aorta and remarked upon their similarity to the specific lesion or Aschoff bodies of the myocardium. Coombs was of the opinion that

<sup>1</sup>For a review of this early work see Bezangon and Weil (45).

familiar with the state of affairs within the thorax before attempting to study this fluid.

The typically rheumatic sero-fibrinous pleural exudate appears as clear or slightly turbid, straw colored fluid and within an hour after withdrawal, a dense coagulum usually forms in which cells are enmeshed, leaving a clear, serous fluid. One is perhaps more impressed with gross evidences of the fibrin content of this fluid at the necropsy table than at the bed side for a glance at the open chest will reveal the presence of small flecks or strings, or in some instances huge masses, which may be either floating or deposited upon pleural surfaces. As most of these masses are too large to penetrate the lumen of the ordinary trocar they do not appear in the usual specimen obtained by aspiration.

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the Aschoff body was essentially a lesion of the coronary arteries and for this reason was to be found only in that portion of the aorta which was supplied by the terminal branches of the coronary arterioles. In discussing this point recently Sacks (9) stated the following

“Inasmuch as the pulmonary artery also receives its blood supply from the coronary arteries, one would expect to find the specific lesions in the outer coats of this artery as well, though perhaps less frequently than in the aorta because of the comparative infrequency of the Aschoff bodies in the right side of the heart.”

As will be shown later in this article this prediction has been borne out by the findings in one or our cases.

We owe the most accurate descriptions of the aortic lesions to Pappenheimer and VonGlahn who have described characteristic dense, acellular, perivascular scars in the media associated with the presence of typical Aschoff bodies in the adventitia (46). Later these authors also described (47) the presence of specific rheumatic lesions in the peripheral blood vessels including those of the lungs, aortic valve, kidney, perirenal and periadrenal adipose tissue, appendix epiploica of the sigmoid colon, ovary, testis, pancreas, etc. They found these lesions in about 20 per cent of their cases, in most of these regions only isolated vessels were affected, but in the lungs in two of their cases practically every small branch of the pulmonary arteries was involved. The lesions were characterized by the exudation of fibrin into and about the vessel, by destructive changes in the cellular components of the vessel wall, by a distinctive cellular reaction in the adjacent tissue and by the absence of thrombosis. The acute lesions were followed by organization with or without the formation of new collateral channels within the thickened intima and occasionally within the muscular layer.

Rheumatic fever is not the only disease which can give rise to changes of this general type and the arteritis of several acute infections has been described by Wiesel and Lowy (48) and others. Nevertheless as our knowledge of this subject increases we are impressed with the fact that such changes are peculiarly prominent in rheumatic fever.

*Main pulmonary artery* Atheroma of the pulmonary artery and its larger branches is a well known finding in cases of long standing

pulmonary congestion especially of mitral stenosis and correspondingly it is a rather common necropsy finding not only in late but also active stages of rheumatism. In one of our cases in which atheroma of the pulmonary artery had been noted grossly, microscopic scars were found in the wall similar to those which have been described in the aorta (46). Typical Aschoff bodies were also found in the adventitial layers of the pulmonary artery as well as in those of the aorta (49), bearing out the prediction made by Sacks to which we have already referred.

*Pulmonary arteries of moderate size* Here the gross and histological picture of the lesion is not so striking as that exhibited by the main trunk or the arterioles. Furthermore the picture does not seem to be particularly specific in nature, rather recalling the changes which have been described by Wiesel and Lowy (48) in the peripheral blood vessels in a variety of acute infections such as influenza, etc. The lesions are only demonstrable histologically and are characterized by slight evidences of cellular degeneration and proliferation in the intimal layer. The medial coat may be thickened, showing irregularity of its architecture largely due to distortion, separation and splitting of the muscular and elastic fibers. Thrombosis of the lumen is a rather uncommon finding.

*Arterioles* Perhaps it is because the changes in the tiny arterioles are more easily detected than in those of larger calibre but in any event the vascular lesions appear to be most prominent here. This is particularly true of the vessel in which the lumen is about equal in diameter to that of a glomerulus. As a rule we have either found many pulmonary arterioles involved or none at all and in our experience such changes have been noted in the lungs in from 20 to 40 per cent of the active cases. Histologically the process has been well described by VonGlahn and Pappenheimer (47). It seems to be essentially a panarteritis in which all of the coats of the vessel suffer, although the most striking changes manifest themselves in the intima and adventitia. Frank obliterative endarteritis has been noted but in our cases we are not sure that the evidence in favor of the endarteritic change being rheumatic is wholly convincing for it is generally found in association with pulmonary atelectasis, which might well be responsible for involutionary changes in the vessels.

*Capillaries* Although the walls of the alveolar spaces may often

be considerably thickened, particularly in those cases of mitral stenosis or long standing chronic passive congestion of the lungs, the actual capillaries within them show relatively little demonstrable change apart from dilatation.

As regards the vascular lesion in general we are struck by the fact that, as in the pleura, it is the endothelium which seems to be primarily involved and this endothelial lesion is associated with a characteristic type of subendothelial perivascular and even interstitial reaction. That there is a relationship between this type of lesion and the well known Aschoff body of the myocardium admits little doubt, although the pulmonary arteritis does not assume the classical picture which is shown by the coronary lesion.

#### LESIONS OF THE LUNG PROPER

It would be difficult to assign any specific pathological picture to the lungs as a whole, in rheumatic fever. It would almost seem like an attempt to assign a specific pathological picture to the lungs in heart disease, or in some chronic infection in which there might be ample opportunity for the occurrence of a variety of insults to the respiratory tract. For example, besides the processes which we have already described, the following gross lesions of the lung proper may occur. Chronic passive congestion, pulmonary edema, differing degrees of pulmonary atelectasis, pulmonary infarction, broncho or lobular pneumonia etc. It is not only difficult to classify such a variegated group of pulmonary lesions but they stand in sufficiently close relationship to those of the heart to make it difficult to discuss one without the other. Nevertheless we can refer to the more important of these so-called complications.

*Pneumonia* Pneumonia is recognized in a somewhat indefinite way, to be a severe although uncommon complication of rheumatic fever. Certainly bronchopneumonia and possibly lobar pneumonia may complicate rheumatic fever or its sequelae at any stage. However, as to whether this pneumonia represents a specific manifestation of rheumatic fever or is merely an intercurrent infection, is still something of an open question.

The uncertainty with regard to the interpretation of the physical signs which occur in the chest in rheumatic fever is probably responsi-

ble for the dearth of accurate statistics on the incidence of pneumonia occurring in an active stage of rheumatic fever. It is said to vary widely in different years and different localities. Apparently the original incidence figures of 11 to 13 per cent which were assembled in England during the middle of the past century by Latham (26) and Fuller (27) are high, whereas more recent German statistics are quite low, such as those of Pribram, who reports an incidence of 0.6 per cent (6), and of Rolly who reports 1.4 per cent (37).

Nevertheless patients with rheumatic fever and particularly those who are most seriously ill may frequently exhibit a clinical picture which simulates lobar pneumonia. These attacks may be heralded by a sharp rise in temperature, with increasing dyspnea, cyanosis and increasing evidences of toxicity. Coughing is a pronounced and troublesome symptom, generally productive of rather tenacious purulent or frothy sputum which is frequently blood streaked or even deeply blood tinged. Furthermore areas of dulness to percussion, bronchial breathing and other physical signs indicative of pulmonary consolidation may be picked up in the chest during an attack. Such attacks may be relatively transient or may last several weeks. As a necropsy finding, however, pneumonic consolidation has been said to be uncommon although there is some confusion on this point.

Thayer (50) has reported a statistical study upon a series of twenty-five fatal cases of rheumatic fever selected from the necropsy series of the Johns Hopkins Hospital. The pulmonary findings are recorded although apparently they were not studied in detail. Terminal pneumonia or bronchopneumonia was noted in 50 per cent of the cases.

Rabinowitz (51), who has recently discussed the question of "rheumatic pneumonia," has concluded that probably a special type of pneumopathy, which is not a true pneumonia occurs during rheumatic fever, that it generally occurs in cases of pancarditis but may occasionally develop independently of arthritis or recent carditis. He suggests that careful histological studies of the lungs in these cases should be made in order to determine whether a specific form of rheumatic pneumonia exists and whether or not Aschoff bodies are present.

An interesting feature in this connection is the occurrence of vas-



cular lesions in the lung to which we have just referred. Eiman and Gouley have considered the relationship of this type of lesion to rheumatic pneumonitis in a recent report (52) and have described certain perivascular and interstitial lesions in the lung which they believe recall the structure of the Aschoff body. Whether or not this disease of the vessels may be associated with an actual pneumonia or pneumonitis is still something of a question, but we have, thanks to this discovery, a hitherto unrecognized lesion, which may be very widespread throughout the lungs

In our attempts to define the diffuse lesion of the lung we have turned to the available necropsy material at our disposal and in a series of 30 cases have noted the following results. In more than half of these cases there were evidences of a focal hemorrhagic lesion, rather widespread, involving individual lobules or groups of lobules, which might be interpreted as an early or hemorrhagic stage of a broncho or lobular pneumoma. This was particularly common in children and in the cases under twenty years of age. Later stages of typical bronchopneumonia, in which were observed scattered patches of confluent lobules showing gross evidences of gray hepatization, were noted in only about 10 per cent of the fatal cases. Whether the first group of cases or those showing focal hemorrhagic lesions are actually manifestations of an intercurrent or terminal bronchopneumonia in its ordinarily accepted sense is a question which we have not been able to answer for there are certain atypical features about the lesion which have served to differentiate it from the usual types of bronchopneumonia, among the most important of which are the extremely hemorrhagic character of the intra-alveolar exudate, together with the difficulty which has been experienced in demonstrating the commoner types of bacteria usually associated with bronchopneumonia. A number of factors may, however, be responsible for this atypical picture, for, as we have previously emphasized, the lung may be already damaged as a result of chronic passive congestion, atelectasis, infarction, etc. Clinically this focal, hemorrhagic lesion is generally associated with fever and hemoptysis, but the degree of consolidation of individual lobules is probably not sufficient to give rise to very appreciable areas of dulness to percussion. We have been inclined to believe that pneumonic consolidation is not as important a factor in the

production of widespread physical signs which are so frequently reported in these chests, i.e., areas of dulness and bronchial breathing, as are other factors, particularly that of pulmonary atelectasis.

It would seem then that secondary broncho or lobular pneumonia in its ordinarily accepted sense or certainly in the sense in which it occurs in the course of certain acute infections such as measles or influenza, is not an outstandingly common finding in rheumatic heart disease. The presence of bronchitis or bronchiolitis on the other hand proves to be an almost universal finding associated no doubt with the ever present evidences of circulatory stasis.

*Passive congestion, atelectasis and infarction* There are, of course, other non specific characteristic pulmonary lesions which occur with great frequency in severe cases of rheumatic carditis. The variety of lesions of this type which occur can hardly be spoken of as being rheumatic, but their frequent presence has undoubtedly been in some measure responsible for the great confusion which existed for more than a century as to the interpretation of the physical signs in the chest in rheumatic fever. The lesions include the usual pulmonary manifestations which we are accustomed to associate with severe forms of carditis such as chronic passive congestion, pulmonary atelectasis due to a variety of causes, and pulmonary infarction. Although non-specific rheumatic lesions in themselves, we should be aware of the fact that whatever injury the virus of rheumatic fever inflicts upon the lungs, such injury may be superimposed upon lungs which are already severely damaged. This consideration should be uppermost in our minds as we attempt to review the pulmonary findings observed in fatal cases.

Coombs (53) has laid great stress upon the influence which the rheumatic cardiac lesions may exert upon pulmonary structure and function. In commenting upon the pulmonary effects of cardiac failure in association with the ever present mitral disease, he emphasizes the degree of stasis which may occur within the pulmonary circulation and which may be accompanied by a rise in pressure resulting in atheroma of the pulmonary vessels.

He also emphasizes another lesion which so frequently plays a rôle in the picture, namely, pulmonary atelectasis, a condition which is frequently encountered in the lower lobes of the lungs. He believes

this to be generally due to compression of the lungs by the rapidly enlarging heart or to reflex immobilization of the diaphragm associated with pericarditis and more rarely to the accumulation of fluid in the pleural cavity. It is evident that the physical signs of pulmonary compression are often erroneously interpreted as evidence of pneumonic consolidation. Coombs (53) may be quoted as saying

“Dullness at the base of the left lung is an almost constant accompaniment of the severest grades of acute carditis. Indeed, its extent is a useful index of the severity of an attack. Sometimes there is a narrow zone of dullness at the extreme right base also, but more usually it is limited to the left side. In front it merges with the enlarged cardiac dullness. Its lower axillary limit is formed by the stomach resonance, which sometimes rises abnormally high. It begins to be noticeable some days after the onset of the attack, and reaches its maximum in about a week, declining slowly from this point as convalescence proceeds; it is only rarely that any relics of it remain permanently. It is associated with diminished and tubular breath sounds, and the chief factor in its causation is massive collapse of the lung due to reflex inhibition of the diaphragmatic movement by pericardial inflammation.”

It seems evident that in accord with the statement by Coombs the finding of dullness to percussion over the base of the left lung accompanied by bronchial breathing, etc., has frequently led in these cases to the erroneous clinical diagnosis of pneumonia. The presence of signs indicative of pulmonary consolidation has proved to be far more indicative of pneumonia if they are found on the right side than at the left base.

Our findings have been in confirmation with the ideas expressed by Coombs although it would seem as if the presence of pleural fluid has also played a very important rôle in the production of pulmonary compression at the bases. Of almost equal importance has been the presence of an enlarged pericardial sac generally in association with frank pericarditis. One cannot over emphasize the relatively enormous size which the pericardium may attain particularly in the juvenile cases, due either to the presence of pericardial effusion, or to the thick sero-fibrinous exudate of a pericarditis with associated edema of the sac wall. Dilatation of the heart may also play a rôle. In the necropsy protocols one finds with great frequency the following com-

ment describing this condition "On opening the thoracic cavity the pericardial sac is found to be enormous almost filling the anterior portion of the left chest. The left lung is not visible being compressed and pushed upwards and posteriorly."

Pulmonary infarction is also recognized as an infrequent but definite complication which may occur during any stage of rheumatic fever but particularly in those cases in which long standing or old cardiac damage has paved the way to the formation of mural thrombi. Widal (5) refers to the occurrence of rheumatic phlebitis which might serve as a source of possible pulmonary emboli.

Chronic passive congestion of the lungs as a result of impaired circulatory efficiency is practically a universal finding in the severer grades of rheumatic carditis. There is nothing particularly unusual about this process except perhaps the fact that frank pulmonary edema is as a rule an uncommon finding. At necropsy most of the lungs while distinctly hyperemic appear dry rather than wet.

#### SUMMARY

We have discussed the pleural and pulmonary lesions which occur in rheumatic fever, which in the past have apparently received more attention from the clinician than from the pathologist. They are probably more common and perhaps of more significance than we have been hitherto led to believe. Among many features they serve to emphasize the rather widespread effects of this disease, of which the cardiac lesions, or in fact the thoracic lesions, are after all, but local manifestations.

We have remarked upon the fact that pleurisy, generally with effusion, is a relatively common lesion of rheumatic fever, particularly in association with cases of carditis generally indicating a severe rheumatic infection. It is perhaps another example of the selective manner in which this disease manifests itself upon serous surfaces. As a rule it is characterized by the accumulation of fibrinous exudate or of an effusion, which, together with the enlargement of the pericardial sac, often with frank pericarditis, is an injurious combination leading to widespread compression of the lungs. This situation coupled with cardiac embarrassment adds considerably to respiratory distress which is such a frequent symptom in this disease.

The presence of histological lesions in the walls of the pulmonary arteries and perivascular spaces has been confirmed as a finding encountered in about 20 per cent of a group of active fatal cases. We have in this process a hitherto unrecognized lesion which may be widespread throughout the lungs.

Frank bronchopneumonia may occur as an intercurrent infection at any stage of rheumatic fever but it is relatively uncommon. The question as to whether a specific form of rheumatic pneumonia exists has been discussed. Many of the cases which we have had the opportunity of studying at necropsy, particularly those occurring in childhood have presented an acute focal hemorrhagic, lobular pneumonia exhibiting certain atypical features which might serve to differentiate them from the usual type of secondary pneumonia. Sufficient evidence has not accumulated to maintain that this lesion is a specific manifestation of rheumatic fever although it seems to be a fairly characteristic finding.

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# A SUMMARY OF PRESENT KNOWLEDGE OF TULARAEMIA<sup>1</sup>

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## DEFINITION

Tularaemia is an infectious disease caused by *Bacterium tularensis*. Primarily it occurs in nature as a fatal bacteremia of wild rodents, especially rabbits and hares. Secondly it is a disease of man, transmitted from rodents to man by the bite of an infected blood sucking fly or tick, or by contamination of the hands or the conjunctival sac with portions of the internal organs or with the body fluids of infected rodents, flies, or ticks.

## HISTORY AND SYNONYMS<sup>2</sup>

Discovered by the United States Public Health Service, tularaemia has been elucidated from beginning to end by American investigators alone.

McCoy in 1911 contributed the first scientific knowledge of the disease by his description of "plague like disease of rodents" which he encountered in the California ground squirrels. McCoy and Chapin in 1912 discovered the causative microorganism which they named *Bacterium tularensis* after Tulare County, California, whence came principally the infected ground squirrels. They furnished serological proof of the infection in two laboratory workers.

Martin, an ophthalmologist of Arizona, had already called attention, by correspondence in 1907, to five human cases occurring in his practice.

Pearse in 1911 described clinically under the title "insect bites" six human cases which he saw in Utah where the disease became popularly known as "deer-fly fever."

<sup>1</sup> Lecture delivered before The Harvey Society November 11, 1927.

<sup>2</sup> For bibliography of 106 references see Francis, E. History of tularaemia, De Lamar Lectures, 1926-1927, Johns Hopkins University.



Vail, Wherry and Lamb of Cincinnati reported in 1914, under "Bacillus tularensis infection of the eye" the first case in man to receive bacteriological confirmation by the isolation of the organism. Wherry also isolated the organism from a wild cotton tail rabbit found dead.

Francis in 1919 and 1920, working in Utah, recognized the identity of "deer-fly fever" and "plague-like disease of rodents" and named the disease tularaemia on account of the presence in the blood of *Bacterium tularensis*. He isolated the organism from seven human cases and from seventeen jack rabbits and, with Mayne, demonstrated the agency of *Chrysops discalis* in transmission.

Parker and Spencer, working in Montana, reported in 1924 the agency of ticks, *Dermacentor andersoni* and *Haemaphysalis leporispalustris* in the maintenance and transmission of the infection. They demonstrated hereditary transmission through the egg of ticks.

Lamb of Idaho in 1923 used the phrase "glandular type of tick fever" in designating cases.

Thompson of Washington, D. C., in 1921 treated a market man who came to him complaining of "rabbit fever". Anti-tularensis agglutinins determined the diagnosis.

Physicians, on reading the recent articles on tularaemia, have now looked backward and plainly recognized the clinical picture of the disease in cases of illness for which at the time no description could be found to fit. Persistence of anti-tularensis agglutinins has proved the correctness of those observations and established the existence of tularaemia in California in 1904 (Johnson), in Arizona in 1907 (Martin), in Ohio in 1908 (Simpson), in Missouri in 1909 (Brosius), in Idaho in 1914 (Lamb and Cromwell), in Illinois in 1914 (Kirkwood), in Wyoming in 1915 (Harris), in Virginia in 1920 (Davidson), and in Louisiana in 1923 (Kerlin).

Ohara in 1925 described a disease of man in Japan contracted from dressing wild hares. This was proven by Francis and Moore to be tularaemia.

#### GEOGRAPHICAL DISTRIBUTION

Naturally infected human cases have been reported from Washington, D. C. and from thirty-nine states of the United States extending from the Atlantic to the Pacific Coast and from the Canadian to the

Mexican border Twenty-five states were added to the list in 1925 and 1926, five in 1927, and two in 1928 The disease was described in Japan in 1925 No other country has recognized the infection

#### ZOOLOGIC DISTRIBUTION IN NATURE

(1) Ground squirrels, (2) wild rabbits and hares, (3) wild rats, and (4) wild mice have been found infected in nature with *Bacterium tularensis*

(1) *The California ground squirrel* *Citellus beecheyi* Richardson was the animal in which McCoy discovered the disease in 1910 His

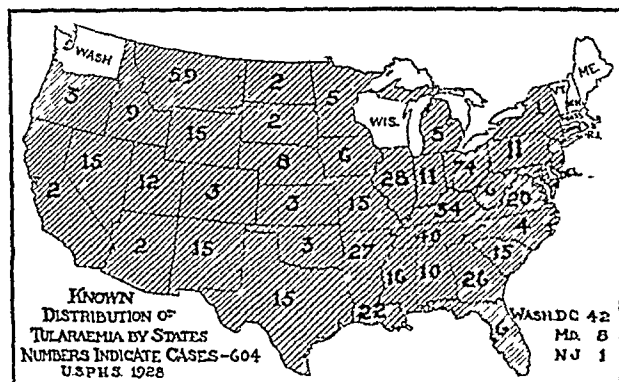


FIG 1

original description was based on a study of forty two naturally infected ground squirrels

(2) *Wild rabbits and hares* Cotton tail rabbits (*Sylvilagus*) jack rabbits (*Lepus*) and snowshoe rabbits (*Lepus bairdi*) constitute the great reservoir of infection Wherry and Lamb cultured *tularensis* from guinea pigs which had been inoculated from two wild cotton tail rabbits found dead in southern Indiana Francis cultured *tularensis* from guinea pigs which had been inoculated with (a) the spleens of seventeen jack rabbits shot or found dead in Utah, (b) the spleen of a snowshoe rabbit found sick in Montana, and (c) the livers of ten cotton

tail rabbits bought in the Washington, D. C., market. Numerous observers have reported sick and dead rabbits in communities where human cases of tularaemia were occurring. Numerous cases of tularaemia have been reported in persons who had dressed wild rabbits only a very few days previous to illness.

Ohara in 1925 reported a fatal disease of wild rabbits in Japan. The heart of a rabbit found dead was used by him to inoculate a volunteer human subject, who contracted tularaemia.

Domestic rabbits raised in rabbitries and sold for food or for laboratory purposes, or to fanciers, have never been found naturally infected, although they are highly susceptible to the infection by inoculation in the laboratory.

(3) *Wild rats*. Dieter and Rhodes, in 1925 while engaged in the routine examination of rats for plague in Los Angeles, California, cultured three strains of *Bacterium tularensis* from guinea pigs into which they had inoculated the tissues of wild rats which had been trapped in the city of Los Angeles. This is the only record of having found the infection in wild rats.

(4) *Wild mice*. Perry, in September, 1927, isolated *Bacterium tularensis* by guinea pig inoculation from two wild meadow mice found dead in Contra Costa County, California, where large numbers of sick and dead mice had been observed. This is the only record of having found the infection in wild mice.

#### TRANSMISSION TO MAN

Transmission of tularaemia to man occurs (1) by the bite of the horse fly, *Chrysops discalis*, (2) by the bite of the wood tick (*Dermacentor andersoni* Stiles), (3) by the bite of a tick (species undetermined), and (4) by contamination of the hands or the conjunctival sac with portions of the internal organs or with the body fluids of infected rabbits, flies, or ticks.

In addition, one case in Montana followed the bite of a coyote (*Canis lestes*). Another case in the same state followed the bite of a ground squirrel (*Citellus richardsoni*). A case in Iowa followed the bite of a hog (*Sus scrofa domestica*). Presumably the mouth parts of the coyote, ground squirrel, and hog were contaminated by infected rabbits which they had eaten, because dead rabbits were found near by readily

accessible One case followed the killing and skinning of a woodchuck (*Marmota flaviventris*) One case followed the scratch of a cat on the cheek There is no report of transmission from ground squirrels, mice or rats to man, although the disease has been known to exist in the California ground squirrel since 1910 The only record of the transfers of infection from man to man is in a case report by Harris in which a mother is believed to have contracted tularaemia through a prick of her thumb, received while dressing the ulcer on her fly-bitten son

(1) Flies of the species *Chrysops discalis* Williston are blood-sucking flies commonly found on horses and cattle, but they also bite rabbits and man Having fed on an infected rabbit they readily infect man at the next feeding, presumably transmitting the infection mechanically by their contaminated mouth parts These flies are found principally in Utah and in the adjoining states

(2) Wood ticks of the species *Dermacentor andersoni* not only transmit the infection from rabbits to man, but, because of hereditary transmission of infection through their eggs to the next generation, these ticks must be considered as a permanent reservoir of infection There is a wide distribution of infection throughout their bodies—in the lumen of the gut, in the cells of the gut wall, in their circulatory fluid, and in their feces They carry the infection over winter, and harbor it throughout their lives They are ideal transmitters of infection These ticks are found principally in Montana and in the adjacent states

(3) Tick bite (species undetermined) has caused 24 cases in Arkansas, Oklahoma, Texas, Louisiana and Tennessee Suspicion is attached to the tick, *Dermacentor variabilis*

(4) Contamination or self-inoculation has caused most of the human cases The specific acts by which man inoculates himself are the following A market man skins and dresses rabbits for his patrons A housewife, servant, or cook dresses rabbits for the table A hunter dresses rabbits at the end of a day's hunt A farmer pulls infected ticks from his horse or cow and then touches his eyes Jack rabbits are skinned and cut up for fish bait, coyote bait, fox feed, chicken feed, hog feed, dog feed, for the table and for the market Persons who have become infected in the laboratory have either performed, or

assisted at, necropsies of infected guinea pigs, rabbits or white mice, or have held infected living rabbits or guinea pigs, or have handled infected living ticks

#### TRANSMISSION AMONG WILD ANIMALS

Blood-sucking insects—lice, flies and ticks—are believed to transmit the infection from rabbit to rabbit in nature, thus contributing to the maintenance of infection throughout all months of the year, and perennially.

#### SEASONAL INCIDENCE

(1) Ticks and (2) flies have a seasonal prevalence, and (3) rabbits are protected by law in certain months

Seasonal incidence of cases of tularaemia is due to the seasonal variation of the three sources of infection—tick bite, fly bite, and the dressing of wild rabbits—but, owing to the overlapping of these influences, cases have occurred in the United States in every month of the year. The great reservoir of infection, and the greatest source of human infection, is the wild rabbit—Jack, cotton tail, and showshoe varieties—but, owing to the agency of blood-sucking insects common to rabbits and man, we also find cases resulting from tick bite and fly bite.

(1) *Tick bite.* March to August are the months recorded for the onset of cases of tularaemia due to tick bite in northwestern United States. These months correspond with the season of greatest activity of the tick *Dermacentor andersoni* which has caused 28 cases in Montana and the surrounding states

February to October has marked the time of onset of 24 cases due to tick bite in southern United States—Tennessee, Louisiana, Texas, Oklahoma and Arkansas. These months correspond with the season of greatest activity of the tick *Dermacentor variabilis* which is provisionally held responsible for these cases

(2) *Fly bite.* June to September are the months recorded for the onset of 23 cases resulting from fly bite and are the months of greatest activity of the horse fly, *Chrysops discalis*, which occurs principally in Utah and the surrounding states.

(3) *Dressing of wild rabbits.* November, December and January

have been the months of onset for 353 cases occurring east of the Mississippi River resulting from the dressing of wild cotton tail rabbits for food. These months embrace the "open season" when, owing to the relaxation of the game laws, the hunting of cotton tail rabbits is generally permitted, and, consequently, these rabbits are then offered for sale in great numbers in the markets.

Jack rabbits are found almost exclusively west of the Mississippi River, and, since they are a pest to farmers they are unprotected by the game laws and their destruction is often rewarded by a bounty. April to October have been the months of onset for most cases west of the Mississippi River, owing to the activities of skinning and cutting up wild jack rabbits for fish bait, coyote bait, chicken feed, dog feed, fox feed, and for the table. Mere contact of the hands with the fur of an unopened rabbit has not caused human infection.

#### OCCUPATION, SEX, AGE, COLOR

Farmers and their families furnish the largest number of cases because their occupation exposes them to ticks, flies, and wild rabbits. Market men, market women, housewives and cooks furnish the second largest group of cases. Hunters and laboratory workers constitute large groups. Single cases have occurred in several professions and occupations. Furriers and workmen engaged in handling dried rabbit furs have not become infected, probably due to death of the infection in the lapse of time between skinning and shopwork.

There were 409 males and 154 females. The oldest was 73 years of age, and the youngest was 2 years. In a series of 603 cases, 38 were negroes.

#### BACTERIOLOGY

*Bacterium tularensis* is a small, pleomorphic organism, Gram-negative, non-motile and non-spore-bearing. It grows only under aerobic conditions. Its optimum temperature is 37°C, and its optimum pH range is between 6.8 and 7.3. It ferments glucose, levulose, mannose and glycerin, forming acid but not gas. It grows well on coagulated egg yolk and blood-glucose-cystine-agar but not on ordinary laboratory media such as plain agar, plain bouillon, gelatin, potato and milk. Bacillary, coccoidal, and bipolar forms are noted. In smears, it stains

well with crystal violet or aniline gentian violet, and in sections it stains best with Giemsa solution. In three of eight attempts it passed through Berkefeld filters which held back a small staphylococcus.

*Heat* A temperature of 56° to 58°C kills the organism in cultures and in spleen tissue in 10 minutes. Thorough cooking renders infected tissue harmless.

*Formalin* Cultures suspended in saline solution containing 0.1 per cent of formalin (37 per cent strength) are rendered non-virulent after 24 hours.

*Trikrisol*. Spleen tissue, rubbed up in 1 per cent trikresol, was free from infection after 2 minutes.

*Glycerin* Pure undiluted glycerin into which cultures or spleen tissue are placed, preserves the virulence 1 month at room temperature, 6 months at 10°C, and 1 year at -14°C. Glycerination in conjunction with annual or semi-annual animal passage serves to perpetuate the virulence of a strain for years.

*Freezing* Spleen tissue frozen at -14°C. loses its virulence in 1 month. Frozen rabbits are infective for 3, but not for 4 weeks.

*Drying* The virus resisted drying in bedbug feces for 26 days.

#### BACTEREMIA

The isolation of cultures from the blood of man during the first week of illness indicates that in man there is a bacteremia early in the disease.

Rabbits, guinea pigs and white mice dying acutely from the infection often manifest a bacteremia so great that 0.00000001 cc. of their heart blood, when injected into a fresh animal, kills acutely with typical lesions of the disease.

The coelomic fluid of the tick and bed bug is rich in microorganisms.

#### SOURCES OF HUMAN INFECTION

##### (1) Ulceroglandular type—416 cases

23 were fly-bitten (*Chrysops discalis*)

28 were tick-bitten (*Dermacentor andersoni*)

24 were tick-bitten (*Dermacentor variabilis*?)

6 were associated with sheep and ticks

4 were bitten by insects (species?)

100 were market men who had dressed rabbits

25 had dressed rabbits bought in the market

- 84 had dressed rabbits which they had shot
- 34 had dissected jack rabbits
- 84 had dressed rabbits the source of which was not stated
  - 1 had killed and skinned a woodchuck
  - 1 was bitten by a coyote
  - 1 was bitten by a ground squirrel
  - 1 was bitten by a hog
- (2) Oculoglandular type—26 cases
  - 18 had skinned or dressed wild rabbits
  - 5 had crushed ticks with their fingers
  - 1 had crushed a fly with his fingers
  - 2 (source of infection was uncertain)
- (3) Glandular type—20 cases
  - 19 had dressed rabbits
  - 1 was an experimental human subject
- (4) Typhoid type—26 cases
  - 20 had autopsied laboratory animals or handled ticks
  - 4 had dressed wild rabbits
  - 1 was tick bitten
  - 1 was probably tick bitten

#### PORTALS OF ENTRY OF INFECTION

(1) *Penetration of the unbroken skin* The typhoid type (absence of primary lesion and absence of lymph node enlargement) has been noted in 20 laboratory workers who autopsied infected animals or handled ticks with bare hands, in 4 persons who dressed wild rabbits, and in 2 persons believed to be tick-bitten. How the infection gained entrance to the body in these cases is unknown. Whether it penetrated the skin of the hands without leaving a local lesion or whether, after contamination of the fingers, the infection was conveyed to the conjunctival sac or to the mouth and swallowed, or whether it was conveyed as a droplet infection remains undetermined. Support for the view that it penetrated the skin of the hands is furnished in the next two paragraphs.

The glandular type (absence of primary lesion but presence of lymph node enlargement) has been noted in 19 persons who dressed wild rabbits and who manifested epitrochlear or axillary lymph node enlargement. This type was also noted in an experimental human subject on the back of whose hand virulent rabbit tissue was gently rubbed resulting in the absence of a primary lesion but with epitrochlear and axillary lymph node enlargement. The portal of entry in these 19 cases must have been distal to the regional lymph nodes.



Experimentally in guinea pigs and rabbits penetration of the normal unabraded, unrubbed and unshaven skin by a virulent culture of *Bacterium tulareense* or by spleen emulsion is a sure method of inoculation which may or may not cause an apparent local skin lesion but which results in fatal infection

(2) *Penetration of the normal conjunctiva* There was no antecedent abrasion of the conjunctiva in 26 cases of the oculoglandular type who had dressed rabbits or crushed ticks or flies with the fingers. Presumably all had transferred the infection to the eyes with their fingers.

Rabbits and guinea pigs are readily infected by minute amounts of virulent cultures of *Bacterium tulareense* gently dropped into the conjunctival sac, care being taken to avoid all irritation.

(3) *Presence of an antecedent abrasion* The presence of an abrasion of the skin, either preexistent or coincident with the time and site of infection, was noted by 137 cases which received their infection from dressing or cutting up rabbits. These abrasions consisted of bruises, cuts, punctures or scratches by fragments of shattered rabbit bone, or by knife, splinter of wood, nail, barbed wire, thorn, briar or burr. In 78 cases which were either fly-bitten, tick-bitten, or bitten by coyote, ground squirrel or hog, the bite constituted the abrasion of the skin.

As to the presence or absence of minute abrasions of the hands, no one really knows even at the present moment whether he has such an abrasion, much less does he know the condition 3 or 4 days ago when he dressed a rabbit.

#### NON-CONTAGIOUSNESS

No instance has been reported of the spread of the infection from man to man by mere contact or by the bite of insects which have previously bitten a patient. Surgeons who have incised or excised suppurating glands have not contracted the infection.

#### PATHOLOGY IN MAN

(1) acute	lesions are noted in man.
(1) <i>Acute</i>	13 and 14
human	at autopsy
found	node
<i>tulareense</i>	in
	onset is the earliest
	sectioned
	ver and lungs
	lesions.

Primary ulcer showed diffuse necrosis with nuclear fragmentation and infiltration with polymorphonuclear leucocytes, beneath which was infiltration with small lymphocytes

Lymph nodes showed focal and diffuse necroses made up of leucocytes, debris and nuclear fragments

Spleen showed on the surface and throughout the pulp, necrotic foci containing amorphous material, nuclear fragments and a few leucocytes, and bordered by normal splenic pulp

Liver contained small focal lesions showing necrosis of hepatic cells, the area being filled with large mononuclear cells, and, where necrosis was advanced, nuclear fragments and polymorphonuclear leucocytes were abundant

Lung showed plaques or small necrotic foci on the pleural surface. Cut section showed small focal necroses or gray broncho-pneumonic patches, or the consolidation involved almost the entire lobe. Microscopically, the alveolar walls showed thickening by edema and by large mononuclear cells, and the alveolar contents were composed of a few leucocytes, red cells, and a small amount of fibrin

(2) *Subacute lesions in man* Subacuteness approaching chronicity characterizes the lesions in man. This applies to the primary ulcer at the site of infection, to the regional lymph glands which drain the site of infection, to the subcutaneous nodules in the course of the lymphatics lying between the ulcer and the glands, and to the internal organs—spleen, liver, lungs and adrenals

In microscopic sections, areas of focal necrosis are seen which show a central necrotic zone surrounded by a layer of epithelioid cells and fibroblasts in radial arrangement, and a peripheral zone of lymphocytes, among which are a few giant cells

The granulomatous type of the subacute human lesions corresponds to the subacute clinical course typical of the disease in man

Pathologists, unfamiliar with the lesions in man, have tenaciously clung to the diagnosis of tuberculosis until forced to give it up by their failure to demonstrate acid-fast microorganisms or to infect guinea pigs with tuberculosis. In such cases the rabbit history and serum agglutination have proved the diagnosis of tularaemia

## CLINICAL TYPES

In studying 614 case reports, four clinical types are noted

(1) *Ulceroglandular type* The primary lesion is a papule of the skin, later an ulcer, and is accompanied by enlargement of the regional lymph glands

(2) *Oculoglandular type* The primary lesion is a conjunctivitis and is accompanied by enlargement of the regional lymph glands

(3) *Glandular type* There is no primary lesion at the site of infection, but there is enlargement of the regional lymph glands

(4) *Typhoid type* There is no primary lesion, neither is there glandular enlargement

## SYMPTOMS AND COURSE

*Incubation* The period of incubation has been definitely determined in 258 cases in which there was a single exposure to infection. In these there was a period of 24 hours in 16 cases, 2 days in 54 cases, 3 days in 73 cases, 4 days in 58 cases, 5 days in 33 cases, 6 days in 11 cases, 7 days in 8 cases, 8 days in 1 case, 9 days in 1 case, and 10 days in 3 cases, the average being  $3\frac{1}{2}$  days. In laboratory workers and market men daily exposed to infection the incubation period could not be determined

*Onset* The onset is sudden, often occurring while the patient is at work, and is manifested characteristically by headache, vomiting, chilliness, chills, aching bodily pains, sweating, prostration and fever

*Ulceroglandular type* These patients complain, within 48 hours after the onset, of pain in the area of the lymph glands which drain the site of infection. On examination, these glands are found to be tender and slightly enlarged. Only the regional glands are involved and not those of other parts of the body. The glandular pain precedes by about 24 hours any definite reference by the patient to the site of infection, which then becomes manifest as a painful, swollen, inflamed papule which breaks down, liberating a necrotic core or plug and leaving an ulcer about  $\frac{3}{8}$  inch in diameter, with raised edges, and having a punched-out appearance. On healing, the ulcer is replaced by scar tissue

There is redness of the skin overlying the enlarged and tender

lymph glands, and this redness may be continuous to the site of infection, or red streaks may be visible on an extremity. In about half of the cases the lymph glands proceed to suppuration, and after the inflammation has subsided an abscess ruptures through a soft, thin spot in the skin. In the other half of the cases the glands do not break down but remain hard, palpable and rather tender for 2 or 3 months, gradually returning to normal. Lymph glands other than the regional glands were slightly enlarged and tender in certain cases.

Lymph glands in such unusual locations as "region of biceps," "mid-arm," "mid-forearm," or "dorsum of hand" have proceeded to abscess formation.

Subcutaneous nodules simulating sporotrichosis were noted on the forearm and arm in 38 cases. They were distributed not only along the vessels on the anterior surface but also over the posterior surface of the forearm or arm, and extended from the ulcer on the fingers to the enlarged axillary glands. The nodules were firm and movable, but many of them ultimately suppurated, they varied in size from that of a pea to 1.0 cm. in diameter, and in number they varied from 2 to 30.

Weakness, loss of weight, recurring chills, sweats, and prostration are often noted during the active stage of the disease which lasts from 2 to 3 weeks.

*Oculoglandular type* These cases follow the general description given above, but with primary localization in the conjunctival sac instead of the skin. Of 26 cases, 23 had unilateral involvement of the eye and glands, 9 being right-sided and 14 being left-sided, 3 had simultaneous bilateral involvement of the eyes and glands. In the early stage the eye manifests irritation, weeping, swelling of the lids and surrounding tissues, edema of the ocular conjunctiva, and usually a papule on the conjunctiva of the lower lid. At the same time there are swelling, tenderness, and pain in some of the following lymph glands: preauricular, parotid, submaxillary, anterior cervical, and, in severe cases, in the axillary group. Small, discrete ulcers appear very soon on the conjunctivae of both lids. The constitutional reaction is manifested by fever, chills, sweating, prostration, and, in severe cases, by convulsions, delirium, and stupor. A purulent dacryocystitis was noted in 2 cases. In half of the cases the glands suppurated. No involvement of the sinuses was noted.

Permanent impairment of vision was noted in only one case, which proceeded to blindness of the affected eye following a perforation of the cornea, protrusion of the iris, and fusion of the cornea and iris into a compact mass

Fulminant cases, running a rapid course, with death, have been noted in the oculoglandular type. The outbreak comprised four members of a family who became ill within a 24-hour period. The symptoms were bilateral in the three who died, but unilateral in the fourth, who survived. Death occurred on the 6th, 8th, and 8th day of illness, respectively. The infection seemed to have been derived from wild cotton tail rabbits. Tularaemia was demonstrated by animal inoculation and by cultural and serologic methods in the survivor, but in the three who died laboratory tests were not made either before or after death, owing to the failure of the attending physician to recognize the condition.

*Glandular type* These are cases which, after dressing rabbits, develop enlarged epitrochlear and axillary glands, but which manifest no lesions on the hands.

*Typhoid type* In this type, fever was the only outstanding symptom. For want of a better diagnosis, attending physicians in these cases have inclined to the diagnosis of typhoid until compelled to give it up by reason of a negative Widal reaction and a positive agglutination of *Bacterium tularensis*. The onset and duration of the disease in this type is the same as in the glandular types.

*Fever* is always present in cases of tularaemia. Complete temperature records are available only for the laboratory cases, and of these charts there are 11. Viewing the 11 charts, one is struck at a glance by the constancy of the sequence of initial rise, remission, and secondary rise. Following the initial fever which lasts 1, 2 or 3 days, there is a remission of temperature for 1, 2 or 3 days, this is followed by a secondary rise to the original height, after which there is a gradual decline to normal, the whole febrile period lasting from 2 to 3 weeks. The early remission of temperature is accompanied by a diminution of all symptoms, and the patient wants to leave the hospital for his home or return to work, but the symptoms return again with the secondary rise of temperature.

*Leukocytosis.* The white-cell count is moderately increased and may reach 16,000, but is not of diagnostic value.

*Skin eruption* A very definite skin eruption was noted in 32 cases. It was macular, papular, pustular, maculo-papular, papulo-pustular, blotchy, or a rash. In some instances it was painful and inflammatory, but was usually painless and did not itch. Desquamation and pigmented remains have been noted. A pustular eruption appeared over the malar bone in an oculoglandular case, the same condition surrounded the ulcer in two cases. Many acne lesions developed on the back of the thorax during the illness in two cases. Extreme herpes was noted in one case. The eruption is bilateral.

*Convalescence* is slow. It is rare for a patient to be at work again at the end of a month. Usually the second month is spent lying about the house owing to weakness on exertion, and during the third month only half-time work is performed. Some have not entirely returned to normal for 6 months or even a year. Relapses of fever lasting 6 and 8 days occurred in two laboratory cases after 10 and 8 months, respectively. Recurring mild attacks of fever have been noted. Suppuration of lymph glands has been noted 6, 8, 10, and even 22 and 24 months after the onset of the disease. Recovery usually occurs without evident sequelae.

*Complications* Broncho-pneumonia was the terminal condition in five cases and lobar pneumonia terminated two. Severe meningeal involvement was indicated in cases manifesting delirium and stupor. General peritonitis was noted in two fatal cases in one of which there was splenic enlargement, diarrhoea, hemorrhages, and some ulcerations of the coecum. Appendicitis developed on the fourth day in one case and required removal. Ascites appeared in one case 3 months after onset, and *Bacterium tularensis* was isolated from the fluid. Coma, accompanied by albuminuria and casts, was the terminal condition in two cases which died at the end of 3 and 5 months respectively.

*Death* Of 654 reported cases 24 terminated in death, the diagnosis having been confirmed by agglutination in nine cases and by cultures in seven others. The duration of illness and terminal condition of 23 fatal cases were as follows:

5 days F W developed delirium and suggestive signs of localized broncho pneumonia of the right lung just prior to death.

6, 8 and 8 days L, C L, and P J L, members of one family, died, two in stupor and one in delirium, within 48 hours of each other.

9 days G D B

12 days J L died with symptoms of general peritonitis

13 days V B was the subject of chronic aortic stenosis and presented the clinical and postmortem picture of bilateral broncho-pneumonia

14 days Mrs J H became semi-comatose on the seventh day

14 days J G F "Flu" was the diagnosis in the first week Lobar pneumonia of the right lower lobe was the diagnosis in the second week and the finding at autopsy

14 days A T R was a typical case of the ulceroglandular type

16 days J C P The "typhoid state" and delirium diverted attention from the true diagnosis of tularaemia at first

16 days W N showed severe constitutional symptoms among which was mild delirium

18 days Mrs C S manifested symptoms of cholangitis and died 18 days after onset and 8 days after an exploratory abdominal incision

23 days "Flu" was the clinical picture in the second week and bilateral lobar pneumonia in the third week

26 days R S Pneumonia of the right upper lobe was the terminal condition clinically

28 days E N, who was the subject of a chronic heart lesion, developed decompensation and died at the end of 4 weeks

29 days L K. During 10 days before death, there were six to eight stools daily and intestinal hemorrhages Post mortem, there was general peritonitis with plastic exudate covering the abdominal contents The spleen was very large and there was some ulceration of the coecum

31 days Patient sat up in bed on the 31st day, developed a precordial pain and dyspnoea and was dead in 20 minutes

34 days T J R passed through a typical course of tularaemia and died on the 34th day

6 weeks B W B Five weeks after onset, bilateral broncho-pneumonia developed, and death ensued 6 days later

8 weeks C H W Bilateral broncho-pneumonia, especially of the lower lobes, developed in the 7th week and death occurred 9 days later

3 months L B died in coma, the last 3 weeks having been marked by general edema and an abundance of albumen and casts in the urine

5 months M C reentered the hospital 24 hours before death in a state of coma and with marked albuminuria

## DIAGNOSIS

Because tularaemia was not borne in mind, the disease has been erroneously diagnosed as follows (1) Clinicians have called it "flu," septic infection, typhoid fever, and sporotrichosis (2) Serologists have called it undulant fever on account of the cross-agglutination of *melitensis* and *abortus* (3) Pathologists have called it tuberculosis on account of the lesions in the lymph glands

The clinician who bears in mind the following tetrad will seldom fail to diagnose a case of tularaemia (1) a history of having dressed or dissected a wild rabbit, or of being tick-bitten or fly-bitten, (2) a primary lesion of the skin in the form of a papule, followed by a persistent ulcer or a primary conjunctivitis, followed often by ulcers of the conjunctiva, (3) persistent glandular enlargements in the region draining the primary lesions, and (4) fever of from 2 to 3 weeks' duration

Having recognized this tetrad in his patient, the clinician will prove his diagnosis (1) by obtaining an agglutination of *Bacterium tularensis* by blood serum collected in the second week of illness and noting an increase in the agglutination titre in serum collected a few days later or in the third week, or (2) by isolation of *Bacterium tularensis* from guinea pigs inoculated with material taken as early as the first week from the primary lesion or from the enlarged glands or the blood of the patient Microscopic examination of cover-glass preparations and cultures taken directly from the patient is useless

## AGGLUTINATION

A study of the blood serums of 584 cases of tularaemia, tested for agglutination of *Bacterium tularensis* showed the following facts

1 There was a complete absence of agglutinins for *tularensis* in the first week of illness

2 Specific agglutinins were always present at some time in the second week

3 There was an abrupt rise in the agglutination titre in the third week which reached its maximum in the fourth, fifth, sixth or seventh week

4 A fall of titre began in the eighth week

5 A gradual diminution in the amount of agglutinins took place until at the end of the first year the average titre of 21 cases was 1:140



6 Specific agglutinins remained for years in the blood of long-recovered cases and did not entirely disappear from any case, even 10, 11, 12, 15, 18, 19 or 24 years after recovery.

I know of no other disease in which an agglutination test will set the diagnosis right in such certain terms after so many years. By the employment of agglutination in conjunction with clinical evidence in 49 cases, Simpson reported in June, 1928, a continuous record of the unrecognized existence of tularaemia in Dayton, Ohio, throughout the preceding 20 years

*Cross-agglutination* Human tularaemia serums may show cross-agglutination of *Brucella abortus* (the cause of contagious abortion of animals) and *Brucella melitensis* (the cause of undulant fever). Of 513 human tularaemia serums so tested, 119 showed such cross-agglutination, while 394 failed, even in dilution of 1 10, many of the latter group were of maximum anti-*tularensis* titre (1280 to 2560).

As a rule, a tularaemia serum agglutinated *tularensis* in much higher dilution than it agglutinated *abortus* or *melitensis*, and the cross-agglutination of the latter organisms was much slower in developing in the water bath. Exceptions to that rule were noted in twelve serums which agglutinated *tularensis*, *abortus*, and *melitensis* to the same, or to nearly the same, degree

The significance of these observations, from the viewpoint of diagnosis, is that a suspected tularaemia serum should be tested, not only for agglutination of *tularensis* but also for agglutination of either *abortus* or *melitensis* unless the clinical history points clearly to the etiology. It has been established by Evans that a serum which agglutinates one of the latter two organisms will also agglutinate the other.

Human undulant fever serums may show cross-agglutination of *tularensis*. Of 48 undulant fever serums so tested, 16 showed some degree of such cross-agglutination, while 32 failed, among the latter group were serums which in dilution of 1280 to 2560 gave agglutination for undulant fever

#### METHOD OF ISOLATING CULTURES FROM MAN

*Bacterium tularensis* has been isolated directly from man by inoculation of culture mediums by Simpson. The organism has not been identified in cover-glass preparations made directly from man. For

TABLE I  
Cross-agglutination

CASE	TIME AFTER ONSET	BAC TERIUM TULA RENSE	BRUCELLA ABORTUS	BRUCELLA MELI TENSI	TREATMENT OF SERUM
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Cross-agglutination by human tularaemia serums

R R S	18 days	640	40	40	Unheated, glycerin
	26 days	1,280	1,280	640	Unheated, glycerin
	7 months	640	320	320	55°C, no preservative
	1 year	320	320	320	55°C, trikresol
	2 years	640	160	160	55°C, no preservative
	3 years	320	160	160	Trikresol, then 55°C
B I T	3 days	0	0	0	Unheated, glycerin
	9 days	80	0	0	Unheated, glycerin
	16 days	1,280	160	320	Unheated, glycerin
	23 days	320	160	320	Unheated, paracresol
	42 days	320	160	160	Unheated, trikresol
	2 years	160	10	10	Unheated, glycerin
E W M	5 days	0	0	0	Unheated, glycerin
	11 days	160	0	0	Unheated, glycerin
	18 days	320	160	160	Unheated, glycerin
	25 days	1,280	320	160	Unheated, paracresol
	71 days	320	80	160	Unheated, trikresol
	87 days	320	80	80	Unheated, glycerin
O P B	5 days	0		0	Unheated, no preservative
	13 days	160	80	160	Trikresol, then 55°C
E W	17 days	80	80	80	Trikresol, then 55°C

Cross-agglutination by undulant fever serums

Dr B S K		160	1,280	1,280	55°C, no preservative
J B W	6 weeks	160	1,280	2,560	55°C, no preservative
L W	1 month	160	2,560	2,560	
	7 months	80	640		
J D		160	2,560	640	56°C, no preservative
L F		80	1,280	320	56°C, no preservative
H P		80	1,280		56°C, glycerin
D Z	1 month	80	2,560		Unheated, no preservative
	7 months	0	160	160	Unheated, no preservative
W O		80	2,560	1,280	Unheated, no preservative

ease of isolation, human tissue is first inoculated into guinea pigs, rabbits, or white mice; culture mediums are inoculated from these animals after they sicken or die

*Animal inoculations* Pus from the site of the fly bite, or tick bite, or conjunctiva, or from other sites of infection, or from the patient's suppurating glands, or tissue from a wild rabbit's spotted spleen or liver should be injected subcutaneously on the abdomen of guinea pigs or rabbits. Such material should first be rubbed in a mortar, suspended in salt solution, and strained through coarse gauze. Blood drawn from the patient's median basilic vein is defibrinated, mixed with an equal volume of normal saline solution, and injected intraperitoneally into guinea pigs. Each guinea pig should receive 4 to 8 cc. of the diluted blood.

Within a week the animals should die, presenting a gray, granular caseation of the enlarged lymph glands and great numbers of small white foci of necrosis studded over the enlarged spleen especially, and over the liver. The organs should be viewed in direct sunlight, or in strong electric light, because the lesions are often minute. The use of a hand lens may be necessary. In the absence of apparent lesions, the death of the animal is sufficient incentive for transfer to a fresh animal.

Material from dead animal's glands, spleen and liver, when rubbed on the shaven, abraded skin of another guinea pig or rabbit, should likewise cause its death within a week with the same typical lesions of the lymph glands, spleen and liver, and thus the infection may be propagated for an indefinite number of passages through guinea pigs or rabbits.

Cultures of *Bacterium tularensis* may be obtained by inoculations of heart blood, spleen, or liver of these animals to coagulated egg yolk or blood-glucose-cystine-agar.

More reliance should be placed on the gross pathologic evidence of the disease in guinea pigs, rabbits and mice than on cover-glass preparations made from these animals.

Spleens of infected guinea pigs or rabbits, if dropped into pure glycerin and placed in the ice box will remain virulent for at least a month, thus affording a means of shipping live virus for identification. Liver is inimical to the life of the infection and should not be placed in glycerin in the same container with spleen tissue.

*Cultures isolated from man* Cultures have been obtained from 23 human cases by guinea pig inoculation as follows

(1) From blood taken during life from 3 patients on the 3rd, 4th and 6th days of illness, respectively, and from blood of 2 other patients taken at autopsy, from the brachial vein in one case on the 14th day and from the heart in the other case on the 14th day Blood taken during life after the 1st week of illness was always negative

(2) From conjunctival scrapings taken from 4 patients on the 4th, 13th, 13th and 17th days

(3) From pus taken from the nose on the 8th day in a case of the oculoglandular type with purulent dacryocystitis

(4) From lymph glands of 9 patients taken on the 5th, 10th, 12th, 14th, 14th, 16th, 17th, 51st and 53rd days Numerous attempts have been made to recover the infection from the pus of lymph glands after the 1st month of illness, but all were negative except two

(5) From the primary lesion on the finger of 3 cases taken on the 5th, 8th and 17th days

(6) From ascitic fluid taken during life, 3 months after onset

(7) From spleen taken at autopsy on the 18th and 26th days

(8) In 1 additional case, cultures were obtained from the finger lesion on the 8th day, from sputum on the 12th day, and from the following tissues taken at autopsy on the 14th day heart blood, spleen, liver and lungs

#### IMMUNITY

One attack confers immunity in man No instance of a second attack has been recorded by practicing physicians Market men who dress rabbits year after year and laboratory workers have had only one attack The long persistence of agglutinins in the blood of recovered patients may be an indication of their immunity

Susceptible laboratory animals (guinea pigs, rabbits, and white mice) have exhibited no evidence of immunity to virulent infection in our laboratory All have died with the single exception of one rabbit, which survived a severe acute attack 35 days following the onset of his attack, he was inoculated subcutaneously with a million fatal doses of a virulent culture and remained well for 21 months

## SUSCEPTIBILITY

Degrees of susceptibility are noted as follows (1) High susceptibility in man, monkey, ground squirrels, rabbits, guinea pigs, mice, woodchucks, opossums, young coyotes, pocket gopher, porcupine and chipmunk (2) Slight susceptibility in rats, cats, sheep and goats (3) Non-susceptibility in horse, cattle, hog, dog, fox, chicken and pigeon

## UNIQUE FEATURES

The following outstanding features of tularaemia deserve special mention (1) The certainty of infection of laboratory workers. (2) The persistence of agglutinins in the blood of long-recovered cases. (3) The cross-agglutination of *abortus* and *melitensis* (4) The granulomatous character of the lesions in man as contrasted with the lesions in animals (5) The cystine requirement of the organism in culture medium (6) Its pleomorphism. (7) Its penetration of the unbroken skin (8) Its invasion of fixed tissue cells—the hepatic cells of a mouse and the intestinal epithelium of tick and bed bug. (9) Its hereditary transmission through the egg of the tick to the next generation of ticks. (10) The great variety of insect hosts (11) The great variety of animal hosts

## PREVENTION

Thorough cooking destroys the infection, thus rendering an infected rabbit harmless for food.

Laboratory workers engaged in performing necropsies of infected animals should wear rubber gloves and should observe all other precautions to avoid infection. Cooks, market men and hunters should wear rubber gloves in dressing rabbits

## TREATMENT

The treatment is symptomatic. Rest in bed is the most important. Those who have had the most experience with the enlarged glands do not advise excision, nor even incision, until a very evident soft, thin place appears in the skin overlying the glands. No preventive vaccine nor curative serum has yet been perfected, nor has any special drug been found effective

## THE METABOLISM OF NERVES<sup>1</sup>

WALLACE O. FENN

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The metabolism of nerves is a subject which has long merited and long lacked an adequate investigation. The new facts which are now rapidly being revealed cannot fail to find their place not only in our attitude toward the specific problems of nerve conduction both peripheral and central, but also in our conceptions of the metabolism of cells in general. The energetics of muscle has served well as a model after which to pattern our ideas of the active metabolism of many another cell. Now we have before us the bare outlines of a new model, the nerve fibre, which is apparently significantly different from the old one in certain details.

The historical aspects of the subject may be disposed of in a few words, sufficient merely to indicate the general status of the problems involved. Undoubtedly the most important fact, which has emerged from all the investigations carried out on nerves, is that this still somewhat mysterious wave of excitation differs fundamentally from most other waves, such as the pulse wave, sound waves, and water waves, in that the energy to which it owes its progress is derived, not from the mechanism or process which initiated the wave at its source but rather from the medium over which it is to pass. We say that it is a self-propagated wave, travelling indefinitely without diminution in intensity. This result was arrived at, however, by indirect reasoning, rather than by direct measurement of any energy changes.

This fact by itself implies, however, that there is an energy expenditure associated with the conduction of a nerve impulse, although in the absence of a direct measurement of this energy change there were many who nevertheless disregarded it or believed that it was negligibly small, and of the same order of magnitude as the energy equivalent of the action current which is only 0.1 per cent to 1 per cent of the total,

<sup>1</sup> Lecture delivered before The Harvey Society, February 10, 1928

according to Hill (Cf. Downing et al., 1926) It was agreed to be sure that nervous transmission fails in the absence of oxygen (von Baeyer, 1903) and even fails sooner when the nerve is stimulated than when it is resting (Thorner, 1909) But this did not prove that the actual process of conduction was oxidative. It did make probable an oxidative removal of waste products which prevented conduction by their presence The further history of the problem, as so often happens, is the history of the development of new and better methods of measurement. Tashiro (1913) with his biometer was the first to perform experiments to which he could point as proof of an extra consumption of energy by a nerve during activity Had his method been a little better he would have convinced those who still felt legitimate doubt. It remained for Parker (1925), using Osterhout's indicator method for carbon dioxide, to show more convincingly that there was an extra output of carbon dioxide during stimulation A. V. Hill (1926) was then able to refine his methods for measuring heat to such a point that he could actually measure the increased temperature of a nerve during stimulation and found it to be only  $7/10,000^{\circ}\text{C}$  per 10 seconds of stimulation. On the basis of such experiments, an increased oxygen consumption during stimulation could be confidently predicted and it was with no great difficulty that I was able to demonstrate this fact for the first time in the summer of 1926<sup>2</sup> Aside from these initial demonstrations of the fact that there is an increased metabolism of nerves during activity, we are most indebted to the work of Gerard, in carrying on the heat measurements with Hill, and later in Meyerhof's laboratory, in confirming my own measurements of the oxygen consumption and adding many important facts, particularly in relation to anaerobiosis and lactic acid formation.

From this short introduction it will be seen that my own part in this revival of interest in nerve metabolism has been but a small one and I do not feel it appropriate that at this time I should attempt an exhaustive and systematic survey of all the recent contributions to this field Instead I must ask permission to develop the subject much as it has presented itself to me, without hesitating to follow up

<sup>2</sup> Winterstein (1907) had previously demonstrated an increased oxygen consumption in the spinal cord of the frog during stimulation, but this result could not safely be applied to peripheral nerve

such side lines as have engaged my attention, with such reference to the important contribution of others as occasion allows

#### THE APPARATUS AND METHOD

In looking about for a method of demonstrating an increased oxygen consumption of nerve during stimulation, I naturally turned to a simple device which I had used for demonstrating a resting oxygen consumption to students. A piece of tissue was placed in a bottle over sodium hydroxide and the bottle was connected to one end of a horizontal capillary tube containing a drop of kerosene. As oxygen was consumed the drop was drawn toward the bottle. I arranged, therefore, a competition between two duplicate nerves, each in a separate bottle, but the bottles connected to opposite ends of the same capillary tube. If both nerves were resting, there should be no movement of the drop. If one was stimulated the drop should show a definite movement toward the stimulated nerve. There was nothing essentially new in the differential volumeter as this apparatus should be called. (See fig 6). It can be used for anything that a differential or single manometer can be used for and it has the added advantages of a very simple calibration and a greater sensitivity without the necessity of using inconveniently small bottles. It is an interesting commentary on the methods of scientific progress to find that essentially this same apparatus was used by Haberlandt (1911) for studying this identical problem. Had he adopted the simple expedient of using a smaller capillary tube, some of the experiments to be described would now be 17 years old.

Figure 1 shows the result of an experiment carried out on the lateral line nerve of a dogfish as used by Parker. The rate of oxygen consumption is plotted here against time. One nerve was in each bottle. The experiment starts with three periods of stimulation of nerve B, an increased consumption of oxygen being indicated by a rise in the graph as plotted. Following this, nerve A in the other bottle is stimulated and the drop moves in the opposite direction, giving a negative rate of oxygen consumption or a fall in the graph. Cross-hatched areas indicate movements due to a heating and cooling at the electrodes on account of the stimulating current. The experiments leave no room for doubt that the oxygen consumption is defi-



nately increased during stimulation and that the absolute amount of this increase is accurately measured. A similar experiment using a frog with both nerves in one bottle is shown in figure 2.

A point of interest in these graphs is the gradual rise of the oxygen consumption to a maximum, followed, at the end of stimulation, by a similar gradual fall to the resting level. This delay might be due to diffusion, it might be due to a delayed consumption of oxygen. The

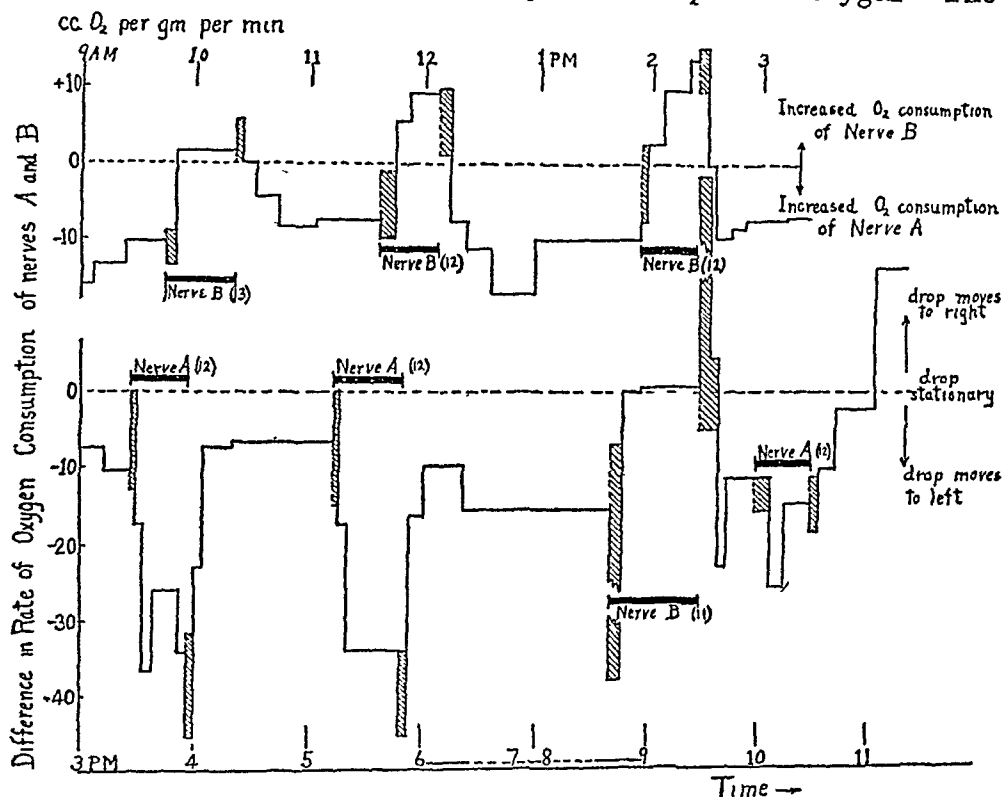


FIG 1 GRAPHS SHOWING THE OXYGEN CONSUMPTION OF DOGFISH NERVES AT REST AND DURING SEVEN DIFFERENT PERIODS OF STIMULATION

delayed consumption in turn might be due to lack of oxygen or it might be due to processes inherent in the nature of the chemical mechanism responsible for conduction. I think that it can be shown that in frog nerve the diffusion of oxygen should be two-thirds complete in about 4 minutes. It might be slightly slower in the larger dogfish nerves. In 20 out of 33 stimulation periods on the dogfish the delayed oxygen consumption lasted 10 to 30 minutes. In the frog the

delayed oxygen consumption is two-thirds complete in 8 to 12 minutes. On the whole, therefore, it appears that *the delay is slightly greater than can be accounted for by diffusion alone*. This conclusion is evidently in agreement with the important observation of Downing, Gerard and Hill (1926) that the heat production due to conduction lasts 9 to 11 minutes after the end of stimulation. As in the case of muscle, therefore, they find a prolonged recovery heat. In nerve, however, only 11 per cent of the total heat comes off in the initial

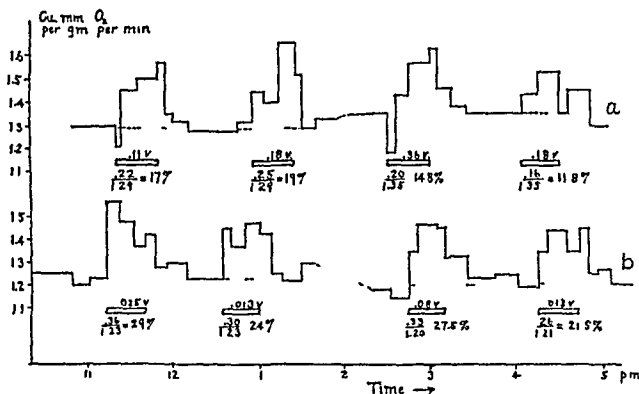


FIG. 2. GRAPHS OF TWO EXPERIMENTS ON FROG NERVES SHOWING THE RATE OF OXYGEN CONSUMPTION AT REST AND DURING STIMULATION AT VARYING INTENSITIES

Figures above the stimulation marks indicate the equivalent voltage of the current derived from the secondary of the inductorium. Below is indicated for each stimulation the percentage increase in oxygen consumption. The magnitude of the response seems to be independent of the strength of the stimulus over a wide range.

phase instead of 40 per cent as in muscle. As a result of this delayed heat production, not only should the oxygen consumption be continued for 9 to 11 minutes after a period of tetanus but it should continue to increase for 9 to 11 minutes after the beginning of tetanus, as in fact it does. After such a period of stimulation therefore, the nerve is the seat of much more intense oxidative recovery processes than at the beginning of stimulation. Hence it is not surprising, as Gerard (1927, c) has emphasized, to find a progressive prolongation of the

refractory period reported by Field and Brucke (1926) To this extent at least a nerve may be said to be fatigable Levin (1927) has also investigated a prolonged electronegativity of nerve after stimulation indicating the persistence of recovery processes

The absolute values which I have found for the excess oxygen per gram nerve per minute of stimulation are somewhat too small (0.32 cu mm per gram per minute instead of 0.8 cu mm) to agree with the heat production due to stimulation as found by Hill and Gerard. One obvious reason for this difference lay in the long periods of stimulation which were necessary for the oxygen determinations while 10 seconds was sufficient for a heat measurement It seemed likely that the nerve would not respond with the same intensity during a half hour as it does during the first 10 seconds Gerard (1927, b) has brought forward evidence to confirm this idea by showing that a greater excess oxygen consumption is obtained, when calculated per minute of stimulation, if intermittent stimulation is used, such as a short tetanus every few minutes When allowance is made for the low temperature at which Gerard worked—15°C instead of 22°C—the excess oxygen which he observed is too high compared to mine, for the absolute magnitudes as measured were identical Likewise the resting rates observed by me were too high (1.2 cu mm per gram per minute instead of 0.27 to 0.45) compared to his even after allowing for the difference in temperature<sup>3</sup> Since errors of measurement in so simple a method seem impossible we must believe in considerable differences between the frogs used It seems, however, probable that when identical material is used at identical temperatures the excess oxygen is sufficient to explain the excess heat production

Having observed an extra oxygen consumption of nerve during activity which is apparently quantitatively comparable to the extra heat production, it becomes important to inquire what relation there may be between the magnitude of this excess oxygen consumption and the number and intensity of the nerve impulses transmitted Such comparisons are laborious to make and the results are never

<sup>3</sup> This is partly (perhaps 25 per cent) to be accounted for by the fact that I weighed the nerves only at the close of the experiment when they were slightly dried whereas Gerard weighed his at the beginning after soaking them in Ringer's solution More recent figures of mine give values of 0.7 to 0.8 cu mm at 20°C

altogether satisfactory because the combined period of stimulation and recovery must necessarily be long in order to be measurable and during that time the nerve may so change its condition that a second stimulation period at a different intensity or frequency may not be comparable. It is nevertheless possible to make out roughly that the excess oxygen consumption is relatively independent of the strength of the stimulus above a certain minimum. (See fig 2)

Significant parallel variations can also be observed by electrical stimulation at varying frequencies as shown in figure 3. In each graph

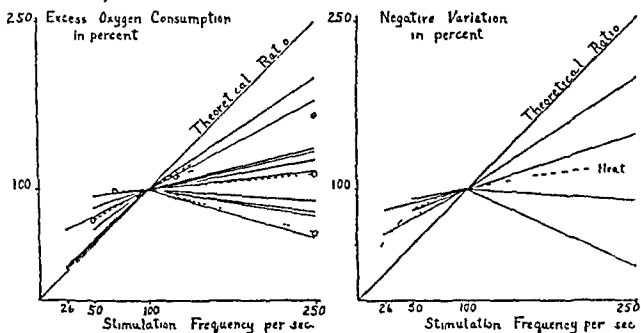


FIG 3 A COMPARISON BETWEEN THE NEGATIVE VARIATION AND THE EXCESS OXYGEN CONSUMPTION IN NERVES STIMULATED AT DIFFERENT FREQUENCIES

In almost every case the nerve was stimulated at 100 per second both before and after stimulation at a comparison frequency to avoid errors due to a change in the condition of the nerve. The dotted line indicating heat is from Gerard, Hill and Zotterman (1927)

the abscissae represent the frequency of stimulation as measured by the frequency of the tuning fork, which was used for interrupting the primary circuit of an induction coil. The response was measured by the increased oxygen consumption, plotted as ordinates on the left, and by the negative variation of the current of injury, on the right. Both the action current and the excess oxygen are plotted in per cent of the figure measured at a frequency of 100 per second. Each radiating line represents the result of two, usually three, alternating half hour stimulation periods at two different frequencies as indicated by the ends of the line. When neither of these frequencies was 100 per

second the line has been extrapolated or interpolated to 100 at the same ratio and is shown dotted. At frequencies greater than 100 the response is less than the theoretical in both cases. At frequencies below 100 it is relatively more than the theoretical. The fact that the response varies with the frequency at all may be interpreted to mean that the expenditure of energy in nerve is discontinuous.

Obviously the frequency is great enough in this experiment so that the nerve cannot completely recover between responses and hence the more rapidly the shocks come the less intense they are. It could easily be shown that the wide variation in the ratio for the higher frequencies was due to variations in the setting of the contact on the tuning fork, thus varying the spacing of the make and break shocks. I apparently did not succeed in avoiding this in long stimulation periods of half an hour. The negative variation was measured by stimulating until a maximum deflection of the galvanometer was obtained (about 20 seconds). In the figure are plotted the most extreme values which could be obtained by varying the setting of the tuning fork and the results are certainly comparable to the oxygen observations.<sup>4</sup>

With an apparatus capable of detecting the heat production of a nerve it is much easier to demonstrate such a parallelism between energy change and functional activity since many observations can be made in a short time. Such measurements were made by Gerard, Hill and Zotterman (1927) and their data for heat production are plotted as a dotted line in the right hand graph for comparison with my results.

Before proceeding to a consideration of the nature of the excess metabolism, the more familiar phenomenon of the resting oxygen consumption deserves brief consideration.

It seems to me of particular interest to consider what it is that determines the rate of oxygen consumption in a resting nerve or other cell. From the foregoing experiments, it is safe to conclude that the excess oxygen consumption is measured by some automatic means

<sup>4</sup> The parallelism between action current and oxygen consumption can be better shown if both are measured simultaneously on the same nerve. I performed a few successful experiments of this type (one of which has been published, 1927, b) but they were interrupted by the breakage of the apparatus and were forsaken later for more important matters.

to meet quantitatively a certain demand for energy Presumably the limiting factor in the chain of events leading to oxygen consumption is something which is characteristically varied during activity If the excess oxygen exactly meets a certain demand it is natural though not necessary, to suppose that the resting oxygen is similarly measured to meet, with similar exactness, a certain need Such an hypothesis is in fact implied in our ideas concerning the basal metabolism of living organisms But it is difficult to believe that all the resting oxygen consumption is indispensable to the life of the cell, for a nerve can be kept in nitrogen for hours, asphyxiated beyond the possibility of conduction, so that its energy supply is, to say the least, very much diminished, and it may still recover almost completely when oxygen is readmitted If some of the resting oxygen is burned, not because it must be burned for survival but merely because the cell "knows how" to do it, so to speak, then the imperative nature of our resting demand for oxygen becomes intelligible only on the assumption that our resting oxygen consumption is better regulated not to exceed our actual needs than is the case in isolated cells

Whatever may control the resting oxygen consumption, it is certainly not the oxygen tension It has been demonstrated by many different lines of evidence that the oxygen consumption at any one point in the tissues is independent of the oxygen tension at that point Assuming the validity of this principle, and knowing (Krogh, 1919) that the permeability of living tissues for oxygen is a little less than half as great as the permeability of water for oxygen, it can be calculated how great the oxygen tension outside a nerve of known dimensions must be in order to supply oxygen to every part of the nerve It appears from such calculations (Tenn, 1927, b) that a comparatively small tension of oxygen is necessary in a frog's sciatic nerve, and that even in the larger dogfish nerves, in air, the oxygen supply would be adequate except possibly in the large end of the very largest nerves where the radius exceeds 1 mm<sup>6</sup> The supply of oxygen is not therefore a limiting factor in these experiments

<sup>6</sup> The maximum possible diameter to be calculated from the weights and lengths of any of the dogfish nerves which I used is 2.6 mm at the large end Gerard is in error in estimating the diameter of some of the nerves in my experiment as 5 mm and interpreting the results accordingly Even 2.6 mm is an extreme figure and takes no account of the flattening of the large end I originally thought, on the basis of preliminary calculations, that diffusion might be a limiting factor

In view of this fact it becomes physiologically significant that nerves isolated from the smaller dogfish show a larger resting oxygen consumption, and even a larger percentage increase in oxygen consumption on stimulation, than similar nerves from larger fish. The variation is in fact roughly proportional to the surface/mass ratio as would presumably be the case in the whole organism. Gerard has con-

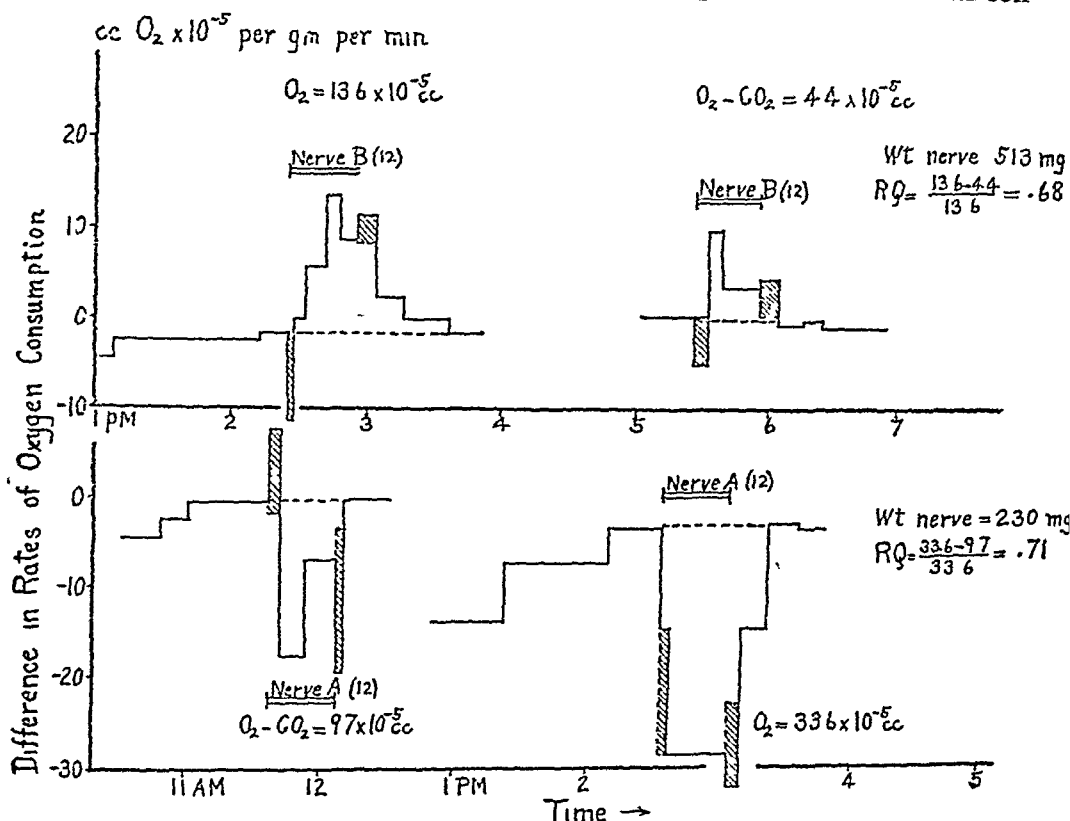


FIG 4 GRAPHS OF TWO EXPERIMENTS INTENDED TO MEASURE THE R.Q. OF THE EXCESS METABOLISM DUE TO STIMULATION OF DOGFISH NERVES

In the upper experiment the oxygen consumption was first measured over NaOH, then the  $O_2 - CO_2$  without NaOH. The reverse order was followed in the lower experiment.

firmed this observation on frog nerves. Wels (1925) has found similarly a larger oxygen consumption in thin sections of tissues from the smaller mammals as compared to the larger mammals. Grafe (1925) found less difference in this respect than did Wels and emphasized particularly the fact that the oxygen consumption of a whole mouse per gram body weight was 33.3 times as great as that of the ox.

while comparable isolated sections of the tissues of the two animals showed that mouse tissues were only 1.7 times as active. This would indicate that the organization of a cell into the whole of a large animal like the ox involved somehow a marked suppression of oxygen consumption.

We may turn next to a consideration of the respiratory quotient of nerves. For the determination of this value I have used first a method, later used also by Gerard, which depended merely upon omitting sodium hydroxide from the respirometer. The inference then is that movements of the index drop indicate differences between the carbon dioxide formed and the oxygen consumed. Experiments of this type always show that the volume in the nerve bottle is diminishing, i.e., the oxygen consumption exceeds the carbon dioxide produced and the ratio between them works out to about 0.8 or even less. An example of the application of this method is shown in figure 4. A nerve is first stimulated in an empty bottle and a small increased rate of movement is obtained. The apparatus is then removed from the bath, sodium hydroxide is introduced, and the nerve is again stimulated in the same way and a larger movement is obtained. The experiment gives figures for both the resting and the excess metabolism. But they are somewhat fallacious, particularly so in very small bottles, because carbon dioxide is accumulating in the bottle and as it accumulates in the bottle it also accumulates in the nerve. Some of the carbon dioxide produced is, therefore, retained. If the carbon dioxide absorption curve for the nerve is known one can apply a correction and so calculate supposedly a true R.Q. Gerard claims to have checked this method by the use of two nerves analyzing one for  $\text{CO}_2$  before and the other after the stimulation period and so determining the amount retained along with the amount excreted. Aside from the assumption that the two sets of nerves used for the original and final analysis are identical, this method is excellent, perhaps the only thoroughly satisfactory one. The fact that he found no different result by this method does not, however, remove the fallacy from the first method which must *necessarily* exist. Moreover, the calculated correction may be large and to obviate this difficulty I have had recourse to another device. This involves putting the nerves in an atmosphere of 10 or 5 per cent carbon dioxide in oxygen instead of



pure oxygen This has the advantage that the extra available base in the nerve is already in the form of bicarbonate so that further increase in  $\text{CO}_2$  tension does not form appreciably more bicarbonate In other words the slope of the  $\text{CO}_2$  absorption curve is less and is more accurately known, so that the correction is smaller, in fact practically negligible

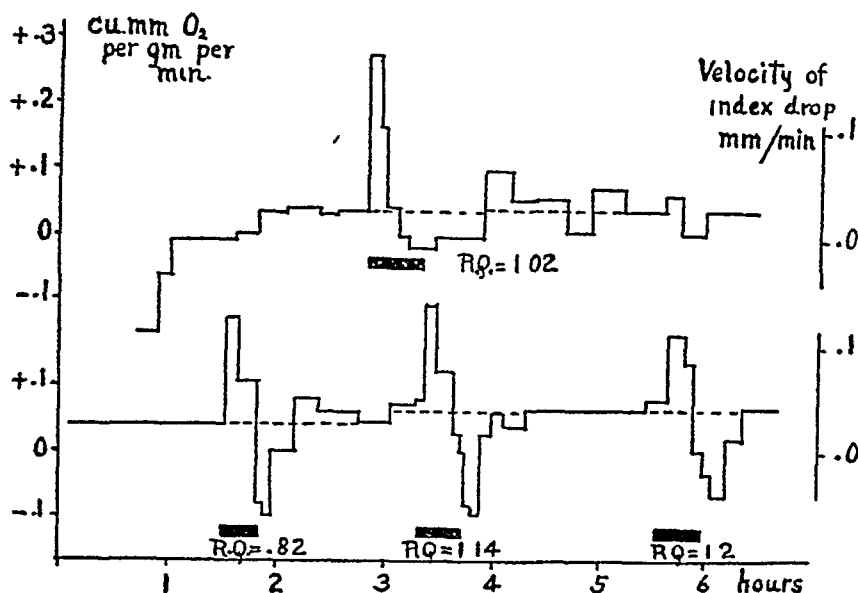


FIG 5 RATES OF OXYGEN CONSUMPTION MINUS RATES OF CARBON DIOXIDE OUTPUT PLOTTED AS ORDINATES AGAINST TIME

The nerves were in an atmosphere of 20 per cent carbon dioxide in oxygen A rise in the curve illustrates a relative increase in the oxygen or a decrease in the carbon dioxide Figures on the graph indicate volumes in cubic millimeters per gram nerve per minute of stimulation corresponding to the areas indicated

The results of experiments on four different nerves, when studied by this method, are shown in figure 5 The first result of stimulation is a decrease in volume (rise of the curve) which is followed by an increase in volume as the carbon dioxide excreted becomes greater than the oxygen consumed It is nearly 30 minutes after the end of stimulation before this increase in volume ceases and the basal rate of volume change is resumed The algebraic sum of these areas above and below the base line gives the net excess change in volume This, subtracted from the excess oxygen, as obtained by a separate meas-

urement, gives the  $\text{CO}_2$  and hence the  $\text{RQ}$ . The average of all the experiments which I have carried out by this method has shown that the increase in volume resulting from stimulation is slightly greater than the decrease so that the average excess  $\text{RQ}$  is 1.19. This is not a figure which it is easy to believe. Frankly I myself find it easier to believe Gerard's extremely plausible value of 1.0. This latter value, however, was not obtained at constant  $\text{CO}_2$  tension which would make it too low rather than too high. I can only be sure that my high values were faithfully observed. Some reaction other than a straight

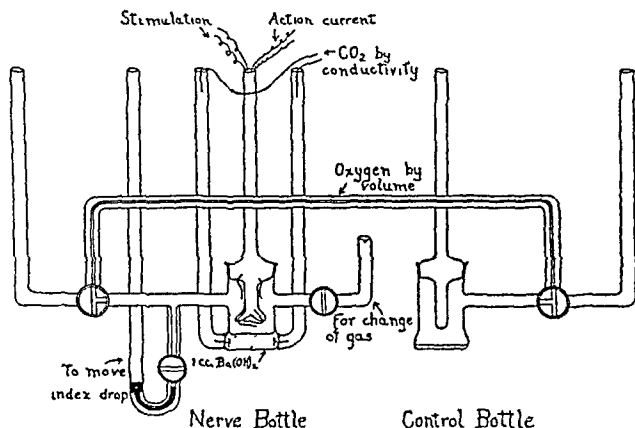


FIG. 6 APPARATUS FOR SIMULTANEOUS MEASUREMENT OF OXYGEN CONSUMPTION BY VOLUME AND OF CARBON DIOXIDE OUTPUT BY CONDUCTIVITY

forward oxidation (such as liberation of preformed  $\text{CO}_2$ ) must have complicated the situation.

But before discussing their possible explanation, I would rather present the results obtained by quite a different method, in which the  $\text{CO}_2$  tension was constant at zero instead of 5 to 20 per cent carbon dioxide. The apparatus (fig. 6) used for this method (Fenn, 1928, a) is a modification of the respirometer previously used. The  $\text{NaOH}$ , however, is replaced by  $\text{Ba(OH)}_2$ . As carbon dioxide is absorbed, barium carbonate is formed and the resulting change in the electrical

conductivity of barium hydrate is followed at desired intervals by means of two electrodes sealed into the bottom of the nerve bottle, and a suitable bridge. The apparatus offers the possibility, therefore, of simultaneous and continuous measurements of both carbon dioxide and oxygen on the same piece of tissue at constant  $\text{CO}_2$  tension

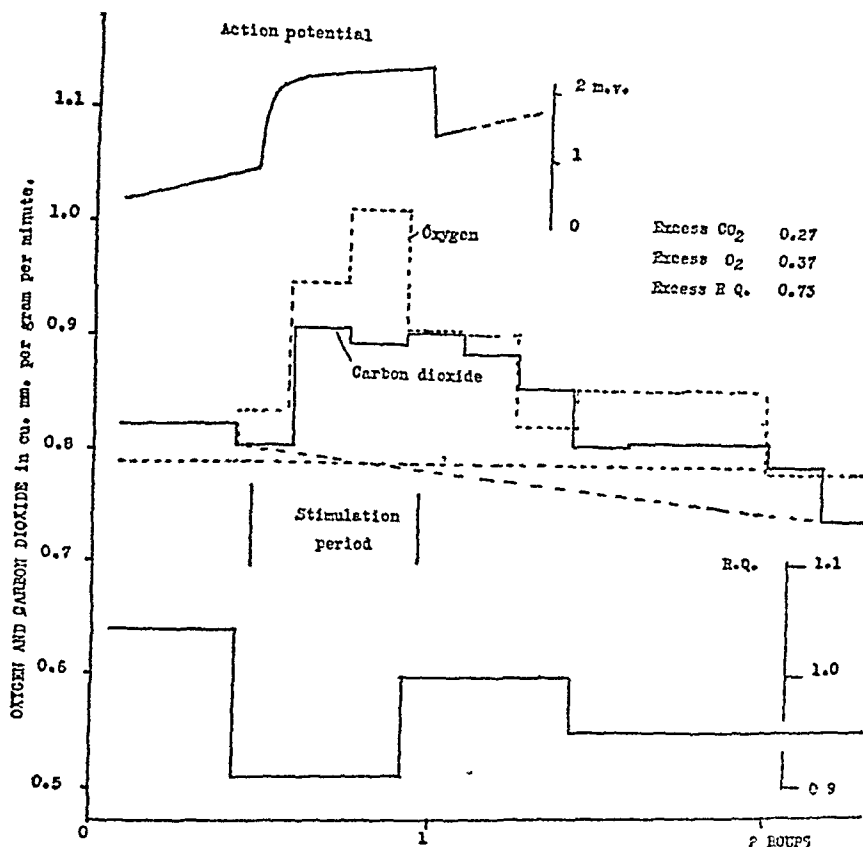


FIG 7 EXPERIMENTS OBTAINED WITH THE APPARATUS ILLUSTRATED IN FIGURE 6

Simultaneous measurement of the oxygen, carbon dioxide and negative variation. Note particularly the initial fall and subsequent rise of the R.Q. of the total metabolism

and has a number of valuable applications. It is of course necessary to have a calibration curve for the barium hydrate, or one can construct such a curve from the cell constant and the published tables of the specific conductivity of barium hydrate. The apparatus is sensitive both as regards oxygen and  $\text{CO}_2$  to 0.02 cu mm as a maximum. Two experiments made with this apparatus are shown in figures

7 and 8 The upper graph in each figure shows the mean change in potential of the intact surface of the nerve during stimulation as compared with the injured end The rates of oxygen and carbon dioxide exchange are plotted in cubic millimeters per gram of nerve per minute The duration of the stimulation, about half an hour, is indicated in the figure, and the increased metabolism during stimu-

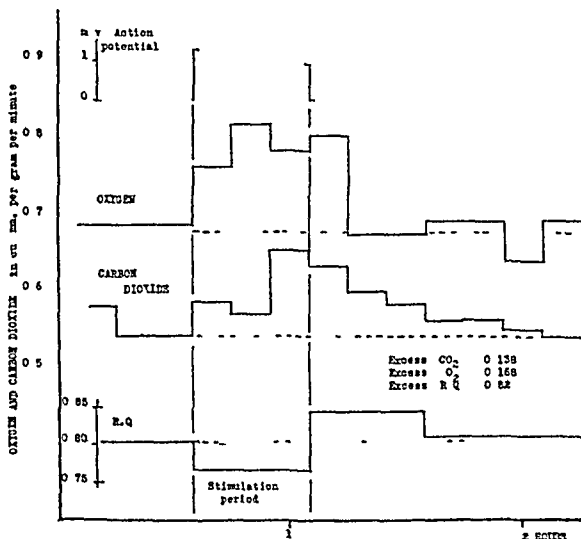


FIG. 8 EXPERIMENTS OBTAINED WITH THE APPARATUS ILLUSTRATED IN FIGURE 6

Simultaneous measurement of the oxygen, carbon dioxide and negative variation. Note particularly the initial fall and subsequent rise of the R.Q. of the total metabolism.

lation is clearly evident. In these two experiments much lower and more reasonable values for the R.Q. were found than in the earlier experiments by the volumetric method. In another experiment similar to these two, however, I observed an excess R.Q. over 1.0, the difference being due possibly to an extra large number of nerves in the bottle. These variations met with in the excess R.Q. lead me to doubt whether it is possible to get an uncomplicated determination of this value.

The resting  $RQ$  of the total gas exchange is plotted in the lowest graph. In both experiments (figs 7 and 8) it shows a tendency to fall at the beginning of stimulation, then to rise above normal toward the end of stimulation. This is independent confirmation of the same series of volume changes which I described by the more direct volumetric method. I postpone for a moment the explanation of this interesting effect.

I find considerable difficulty in summing up our information concerning the  $RQ$  of nerve. Gerard quotes a figure of 0.77 for the *resting*  $RQ$  of nerves from winter frogs. Most of the values which I have obtained are between 0.9 and 1.0 and, in fact, the average of all my figures by the volumetric method was 0.97. An average, however, conveys a false sense of accuracy. By the conductivity method it is possible to measure the variations in the  $RQ$  from one 10-minute period to the next. Quite typically the  $RQ$  starts at 1.5 or 2.0 and gradually diminishes during the next 8 hours, finally reaching a value between 0.8 and 0.9. Parker (1925) described a "gush" of carbon dioxide when a nerve is first dissected and a similar gush following injury. This obviously agrees with a high initial  $RQ$ . This gush is not altogether due to a gradual equilibration to a lower  $CO_2$  tension because I have observed a similar initial increase in volume lasting several hours in the respirometer in an atmosphere of 20 per cent  $CO_2$  (Cf fig. 5). It would naturally lead one to prophesy an initial formation of lactic acid, but Gerard and Meyerhof (1927) were unable to detect any such change by direct analysis of nerves supplied with oxygen. Although the possibility of an acid formation under the conditions of Parker's experiments and mine (particularly a temperature of  $22^\circ$  instead of  $15^\circ C$ ) is perhaps not thereby excluded, there remains also the possibility of an oxidizing reserve, much of which might be used up soon after dissection, involving a loss of carbon dioxide without a corresponding oxygen intake. It seems, therefore, that no single figure can encompass all the analyses of the fumes from a chemical laboratory as complex as that found in a live nerve.

As already stated, in order to correct for the carbon dioxide retained as the tension mounts inside the respirometer, it is necessary to know the shape of the  $CO_2$  absorption curve for the tissue. We have been made familiar with such curves for blood by the publications of many

investigators, notably those of your president (Van Slyke, 1921) It has seemed of interest from a general point of view, therefore, as well as being essential for my own experiments, to measure a similar  $\text{CO}_2$  absorption curve for nerves I have used both a conductivity method and a volumetric method for this purpose (Fenn, 1928, b) In the volumetric method the tissue is equilibrated with oxygen in one bottle of a differential volumeter The oxygen is then quickly flushed out with a known mixture of  $\text{CO}_2$  and  $\text{O}_2$  for perhaps 5 seconds with mini-

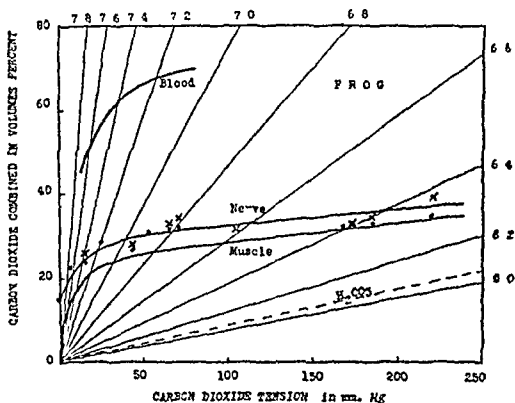


FIG 9 A COMPARISON OF THE CARBON DIOXIDE ABSORPTION CURVES FOR EQUAL WEIGHTS OF NERVE, MUSCLE AND BLOOD OF THE FROG

Figures for the blood are taken from Wastl and Selykar (1925) Figures for nerve and muscle indicate cubic centimeters per 100 grams

imum change of temperature or vapor pressure The cocks of the respirometer are then quickly turned again and volume readings resumed As carbon dioxide is absorbed by the tissue, the diminution of volume is recorded by the movements of the index drop By observation of the index drop one can observe both the rate of diffusion of carbon dioxide into the nerve and the total amount absorbed From the rate one can calculate the diffusion coefficient of carbon dioxide in the nerve (as I shall show later) and from the total amount one can plot the carbon dioxide absorption curve of the nerve and de-

duce perhaps the internal pH. Such a curve is shown in figure 9. A similar curve for frog muscle, obtained in the same way, is plotted for comparison, as also a curve for frog blood taken from the experiments of Wastl and Seliškar (1925). It is evident that the nerve has about the same alkali reserve as muscle although it is not called upon to neutralize any considerable amounts of lactic acid in its ordinary activities. Compared with an equal volume of blood the tissues show a very low  $\text{CO}_2$ -combining power. A very similar difference between the slopes of the  $\text{CO}_2$  absorption curves of blood and tissue was observed by Shaw (1926) by a procedure equivalent to titrating a whole cat with carbonic acid, with the  $\text{CO}_2$ -combining power of the blood separately determined. By quickly killing a resting frog, removing one gastrocnemius muscle and grinding it up under acid in the conductivity apparatus which I have described, the normal carbon dioxide content can be found. By comparison with the  $\text{CO}_2$  absorption curve the  $\text{CO}_2$  tension inside the muscles at rest can be estimated. The value obtained is about 20 mm Hg. At this tension the pH inside the cells of nerves and muscles should be about 7.4. Analysis of fatigued muscles in a similar way shows that at a  $\text{CO}_2$  tension of 20 mm Hg they would have a pH of about 6.7. Muscles in heat rigor lose practically all their combined  $\text{CO}_2$  and have a pH in the neighborhood of 6.0. Stimulation of nerves does not produce measurable changes in the alkali reserve nor have Gerard and Meyerhof been able to demonstrate an accumulation of acid during stimulation.

From the rate of diffusion of carbon dioxide into a nerve as measured by observation of the index drop in the respirometer after sudden introduction of  $\text{CO}_2$  it is possible to calculate the diffusion constant of  $\text{CO}_2$  in nerve tissue. This is done by the formula of Andrews and Johnston (1924)

$$(1) \quad \frac{Q}{Q_1} = 1 - 4 \left\{ \frac{1}{5.783} e^{-\frac{kt}{a^2} \times 5.783} + \frac{1}{30.47} e^{-\frac{kt}{a^2} \times 30.47} + \text{etc} \right\}$$

which expresses the percentage of diffusion,  $Q/Q_1$ , which is complete in time,  $t$ , in terms of  $a$ , the radius of the cylinder and  $k$  the diffusion constant. Since  $kt/a^2$  is a number without dimensions, it follows that  $k$  has the dimensions of  $\text{cm}^2/\text{sec}$ . Applying this formula to the case of the diffusion of carbon dioxide into nerve, it is found that the ex-

perimental values can be predicted fairly well, as shown by the example in table 1. Knowing the diameter of the nerve one can then calculate the value of  $k$ , as shown in table 2. These may be regarded as approximate figures only, but good enough to justify comparison with other figures to be found in the literature. This is the first direct determination of this value to my knowledge but diffusion constants for  $\text{CO}_2$  and  $\text{O}_2$  in other materials are available and are collected in table 3. Krogh (1919) alone has attempted measurements of this sort in living tissues but what he actually determined was the permeability of tissues, to oxygen chiefly, and in one determination to carbon dioxide. The permeability depends upon the solubility

TABLE 1  
*Rate of diffusion of carbon dioxide into nerve*

TIME  minutes	PER CENT NOT ABSORBED	
	Calculated	Observed
0	100	100
1	63	64
2	50	49
3	41	39
4	34	32
5	28	28
6	24	24
10	12	15
25	4	7

and so is much greater for  $\text{CO}_2$  than for oxygen. To obtain diffusivities from Krogh's figure, therefore, I have had to estimate the solubility and divide his figures by my estimate. The rate at which a nerve becomes saturated at a given tension depends, however, on the rate with which any one molecule will diffuse, i.e. the diffusivity or  $k$ . The more soluble a gas is in the nerve, the greater the number of molecules which must diffuse in. Hence a greater solubility does not increase the rate of saturation. As the table shows, the diffusivity of oxygen is greater than that of carbon dioxide, the rate varying theoretically inversely as the square root of the density. This rule when applied to water and rubber, is nearly correct but in living tissues  $\text{CO}_2$ ,



diffuses relatively too slowly according to my figures. This is probably due in part to the fact that much of the  $\text{CO}_2$  in the nerves is ionized and as such does not diffuse readily across cell boundaries

TABLE 2  
*The diffusion coefficient of carbon dioxide in nerve*

EXPERIMENT	PER CENT $\text{CO}_2$	$k \frac{\text{CM}^2}{\text{MIN}}$
1	8 5	$7.1 \times 10^{-5}$
2	9 3	6 7
3	3 1	3 7
4	24 2	8 4
5	29 2	9 6

The tendency for  $k$  to increase as the per cent  $\text{CO}_2$  increases probably depends upon the fact that under these conditions relatively less of the total  $\text{CO}_2$  in the nerve is combined, and hence less readily diffusible

TABLE 3  
*Diffusion coefficients in  $\frac{\text{cm}^2}{\text{min}}$  of oxygen and carbon dioxide in various substances*

MEDIUM	TEMPERATURE	OXYGEN	CARBON DIOXIDE	
	$^{\circ}\text{C}$			
Water	16	$113 \times 10^{-5}$	$95 \times 10^{-5}$	Hufner, 1897
Rubber	17	5 7	5 1	Daynes, 1920
Connective tissue	20	37	20-27	Krogh, 1919
Muscle	20	45	—	Krogh, 1919
Muscle	22	—	11 7	Fenn, 1928, b
Nerve	22	—	7 1	Fenn, 1928, b
Theoretical ratio	—	1 18	1 0	Inversely as $\sqrt{\text{density}}$

The figures of Hufner and of Daynes have been multiplied by  $\frac{1}{1440}$  and 60 respectively to change the units to minutes. Krogh's figures have been multiplied by  $10^{-4}$  to change microns to centimeters and divided by the absorption coefficient. For oxygen this was taken to be 0.0314, the value for water at  $20^{\circ}\text{C}$ . For  $\text{CO}_2$  I have taken a value of 1.5 to 2 estimated from my curves for muscle (fig. 5).

The fact that the amount ionized (or combined) varies with the tension is another complicating factor.

This digression concerning the carbon dioxide absorption curve and the diffusion coefficients of the respiratory gases has been a neces-

sary preliminary to an explanation of the peculiar volume changes which have been shown to occur in the atmosphere surrounding a stimulated nerve, resulting in an initial decrease and subsequent increase in the volume and hence in the R Q. The experiments showed in particular a tendency to a sudden fall in the curve (increase in volume) immediately after the cessation of stimulation, as indicated by the black marks. These volume changes are not artefacts due, for example, to lag in taking up of  $\text{CO}_2$  by the NaOH, because in this experiment  $\text{CO}_2$  is not taken up. The phenomenon is not an artefact due to some complication around the stimulating electrodes because it occurs likewise with approximately the same time relations in stimulated muscles where the stimulus lasts only a few seconds (Fenn, 1927, d).

When a nerve is stimulated the gas diffusion problem is the same as if the nerve were suddenly exposed to a higher oxygen tension and to a lower carbon dioxide tension. Each gas must diffuse according to the gradient produced until a new equilibrium is reached. The time necessary to reach this new equilibrium will depend upon the dimensions of the nerve and upon the diffusivity of the gas. The greater diffusivity of oxygen is evidently in the right direction to explain the initial decrease in volume observed, i.e., it would cause the oxygen to be absorbed before the corresponding carbon dioxide was eliminated.

It has seemed worth while to elaborate this explanation a little by a calculation of the theoretical volume changes for a 30-minute period of stimulation. For this purpose it was assumed that the rate of diffusion of each gas could be expressed with sufficient accuracy for the purpose by the first term only of formula (1), or by the simple exponential equation,  $V = V_{0e} - \frac{t}{T}$  in which a high diffusivity appears as a small time constant,  $T$ . This is the time at which all but  $1/e$  of the diffusion is complete. For carbon dioxide the time constant is 6 minutes, which corresponds to the diffusivities given in table 2. As is obvious from table 3 it is by no means certain just how much smaller the time constant for oxygen should be. Assuming, however, a time constant for oxygen of 3.7 minutes it is easy to calculate for every time,  $t$ , after stimulation begins, how much carbon dioxide will have been

eliminated and how much oxygen will still remain unabsorbed. The sum of these two is the volume outside the nerve. By calculating these volumes for each minute of the 30-minute period of stimulation and adding the results together the total rate of volume change outside the nerve is obtained and the result is plotted in figure 10 for comparison with the experimental curves. The result varies, of course, with the  $R/Q$  and two different  $R/Q$ 's have been plotted. The main features of the experimental curves are fairly well reproduced. It can hardly be said, however, that the calculation is sufficiently rigid to demonstrate that the assumed ratio between the diffusion constants of oxygen and  $CO_2$  is the correct one or to preclude the possibility of some actual delay in the appearance of carbon dioxide, as an alternative explanation.

In a sense, however, all these matters are mere details in the physiology of a nerve. The same principles must certainly apply in the body but the diffusion distances here are so small that probably no delay in the appearance of  $CO_2$  could be actually observed. As far as the physiology of a nerve impulse is concerned, I have added so far only one more demonstration of the fact that the conduction of a nerve impulse involves a definite breakdown of energy in the nerve fibre over which the impulse passes. Is anything known as yet concerning the nature of the breakdown? Is it similar to the energy cycle of skeletal muscle? Although this muscle cycle is now so familiar that it has become one of the corner stones of biological science, I nevertheless venture to interject here a description of an experiment (fig 11) on the energetics of muscle merely because it illustrates this mechanism more completely, I think, than any other single experiment, and also illustrates another application of a new experimental method which I have described. For this experiment I am indebted to the collaboration of Mr. D. S. Martin of my laboratory.

The experiment involves the simultaneous direct and indirect calorimetry of the isolated sartorius muscle of the frog. The apparatus resembles in principle that already shown for nerve. Oxygen is determined volumetrically by the movements of a kerosene drop. Carbon dioxide is determined by conductivity. A thermopile is included in the respirometer bottle by means of which the initial and recovery heat production of the muscle after a short tetanic stimulation are

recorded. The measurements made on a single muscle during a whole day are plotted, including three stimulation periods of about 10 seconds' duration each. At the bottom are plotted the rates of oxygen consumption and carbon dioxide output as marked. Above are plotted the RQ of the total metabolism and the galvanometer deflection throughout the day. The latter is calculated into calories by means of a calibration of the dead muscle by an alternating current of known strength as in Hill's method. The maximum deflection indicates the

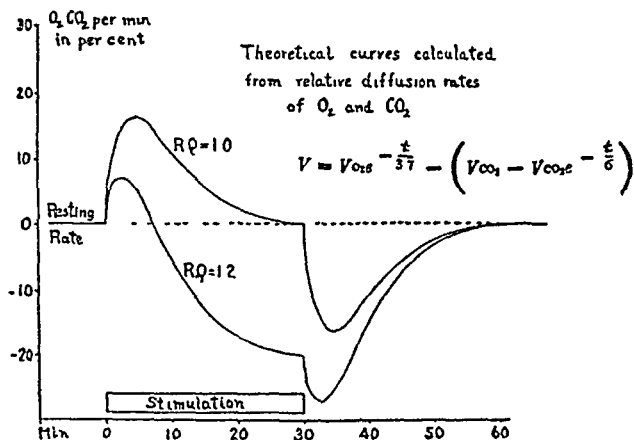


FIG. 10. THEORETICAL RATES OF VOLUME CHANGE OUTSIDE A NERVE FOR COMPARISON WITH THE EXPERIMENTAL RATES AS ILLUSTRATED IN FIGURE 5.

initial heat, while the total area under the curve represents the total heat, initial plus recovery. Only after the first period of stimulation was the recovery sufficiently complete to admit of calculations. Here the excess oxygen represented an energy equivalent of 0.071 calories while the excess carbon dioxide was 0.075, with an excess RQ of 1.05. It is assumed in calculating calories that lactic acid was being burned. Direct calorimetry, i.e. the area under the first galvanometer deflection, indicated a total heat of 0.069 calories, which is as good a check as the method permits. From the initial heat, it is possible to

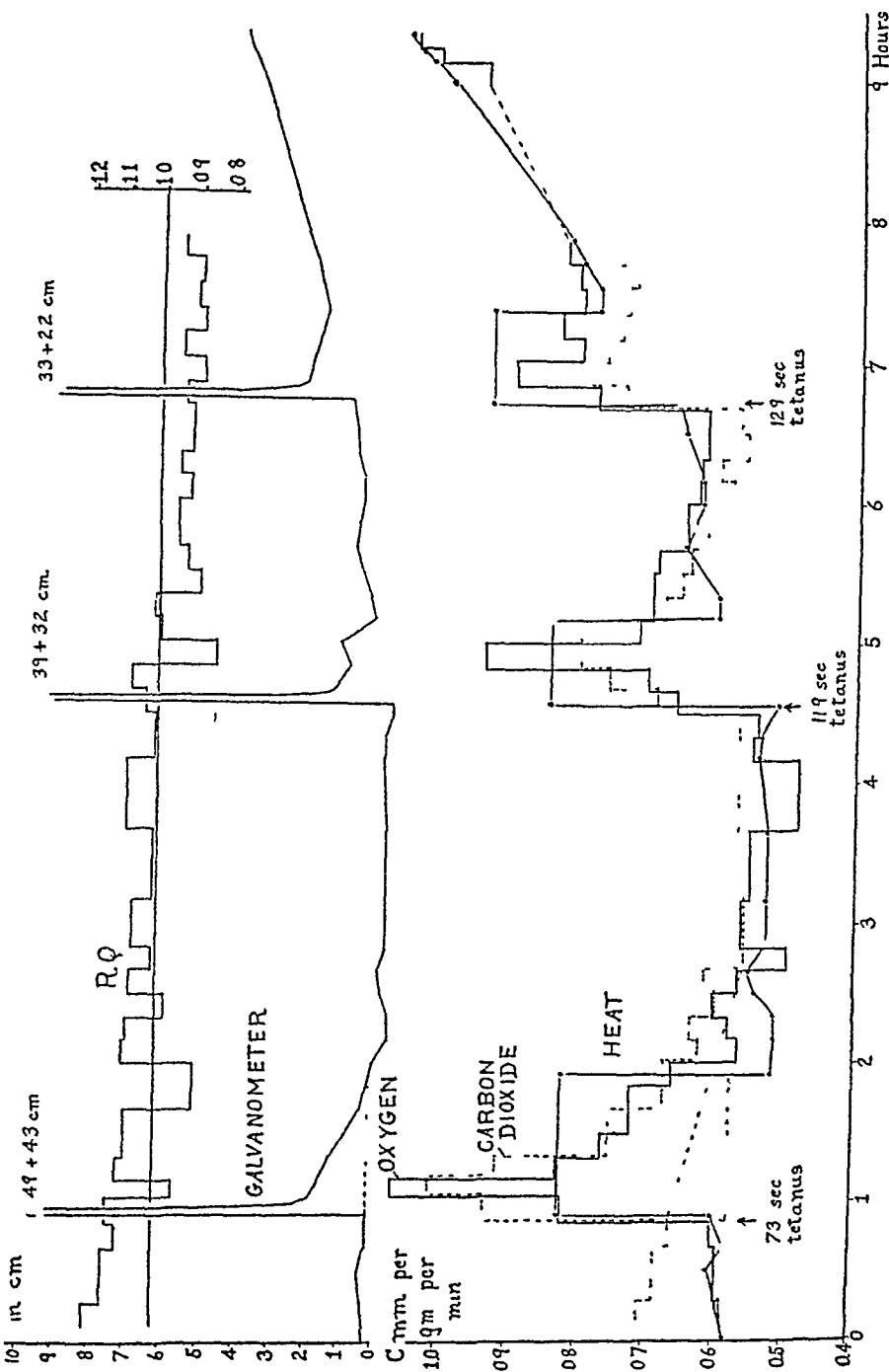


FIG 11 SIMULTANEOUS MEASUREMENTS ON THE ISOLATED SARTORIUS MUSCLE OF THE FROG (WEIGHT 140 Mgm) OF OXYGEN CONSUMPTION, CARBON DIOXIDE OUTPUT, INITIAL HEAT AND RECOVERY HEAT DURING REST AND STIMULATION

Excess RQ = 1.05, excess  $O_2$  = 0.071 calorie, excess  $CO_2$  = 0.075 calorie Total heat = 0.069 calorie, initial heat = 0.034 calorie, recovery heat = 0.035 calorie Lactic acid formed = 0.097 per cent, equivalent oxidized = 0.021 per cent, per cent oxidized = 21

calculate how many grams of lactic acid were formed and it is found that there was formed about five times as much as could be oxidized by the oxygen consumed, so that only 21 per cent or its equivalent was actually oxidized, the remainder having been removed in some other way. Had it not been removed, the total heat would have been greater than the energy equivalent of the oxygen. The method provides, therefore, a check on the accuracy of the calibration and on the completeness of recovery. The second period of stimulation showed failure to return to the base line and the third period of stimulation precipitated rigor mortis (presumably). To show how well the direct heat measurements followed the oxygen consumption it has been assumed that both agreed just before the first stimulation period, i.e. the true galvanometer zero has been calculated from the resting oxygen consumption, using the electrical calibration of the dead muscle as a basis. Thus the galvanometer readings can be expressed in cubic millimeters oxygen per gram per minute and they have been so plotted. The accuracy with which they agree with the oxygen and  $\text{CO}_2$  measurements indicates that all the heat can be accounted for by oxygen. It is interesting to find that lactic acid can accumulate without more effect upon the carbon dioxide, since the  $R/Q$  falls steadily during the experiment, as it does in nerve. This is chiefly related to the fact that the carbon dioxide tension is zero in the respirometer, so that the amount of preformed bicarbonate is at a minimum. Most of the lactic acid is, therefore, neutralized otherwise than by the escape of carbon dioxide.

It would be desirable but exceedingly difficult to do this same experiment on a nerve. Instead we must look elsewhere for evidence to find out whether the energy cycle of a nerve in activity resembles that of muscle. This question is best answered in connection with the behavior of a nerve under anaerobic conditions. The following experiment (fig. 12) will serve to introduce the discussion of this question. The apparatus used is that already described, permitting simultaneous measurements to be made of the oxygen consumption by volume, of the carbon dioxide by conductivity and of the negative variation. Stop cocks in the nerve bottle permit a rapid change of gases. The nerve is dissected out and placed on the electrodes in the nerve bottle. The apparatus is full of room air at the start and

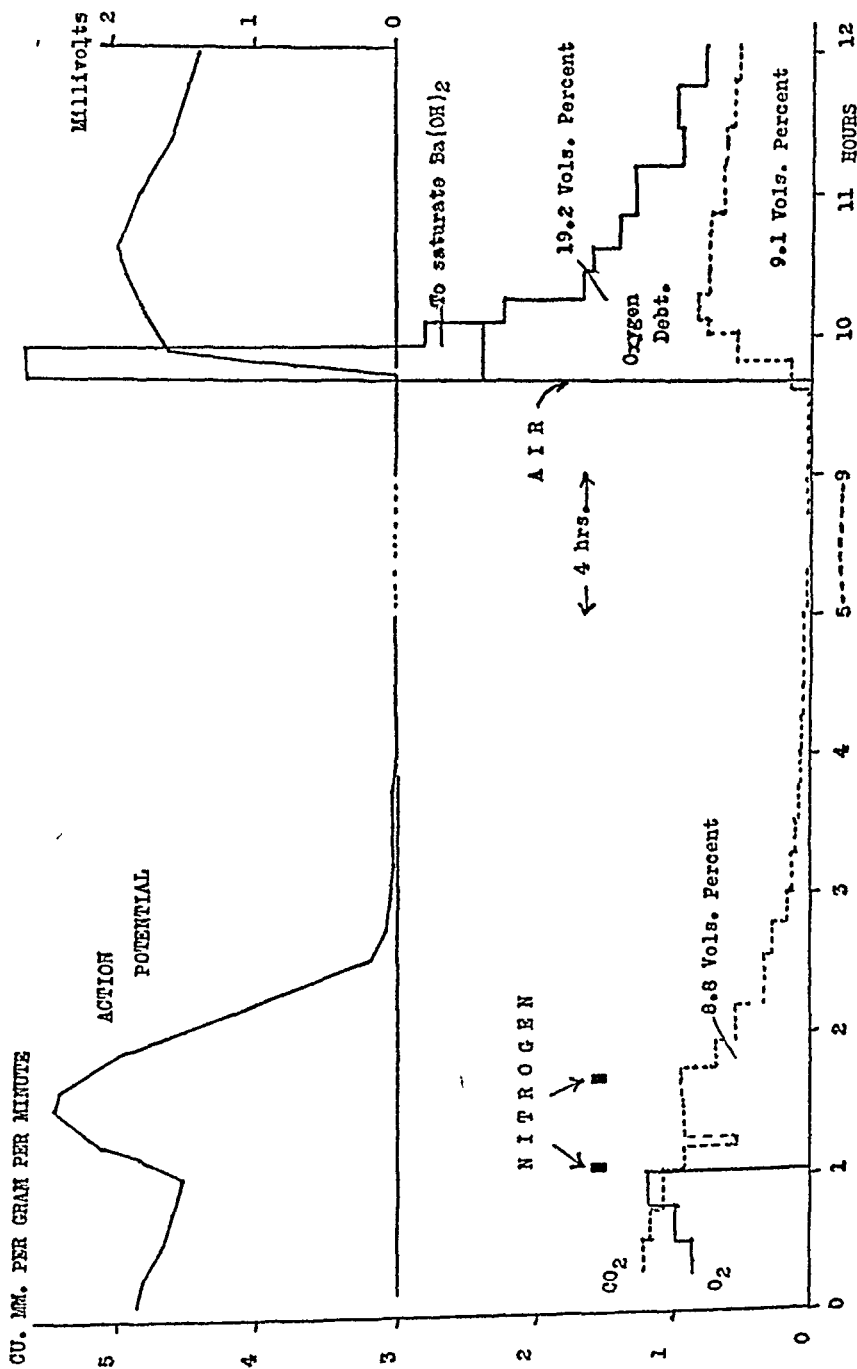


FIG 12. SIMULTANEOUS MEASUREMENTS OF THE OXYGEN CONSUMPTION, CARBON DIOXIDE, OUTPUT AND NEGATIVE VARIATION OF NERVES DURING ANAEROBIOSIS AND RECOVERY THERIOM

Note particularly the loss and recovery of conduction as shown by the galvanometer, the excess oxygen consumption after anaerobiosis and the maximum in the carbon dioxide curve during the oxidative recovery

measurements are made of the oxygen and carbon dioxide exchange. The nerve is electrically stimulated at intervals of 10 minutes and the resulting maximum deflection (for continuous stimulation) of the galvanometer is read to obtain the negative variation. After about an hour, air is replaced by a stream of nitrogen, purified by passing over heated copper and conducted through glass tubes and two short mercury-sealed rubber joints. It is passed through the chamber for perhaps 5 minutes with gentle shaking of the apparatus to assist in the removal of oxygen from the barium hydrate. After a 15-minute period, during which the carbon dioxide output is measured, nitrogen is passed through again to make sure that all oxygen which diffused out of the barium has been removed. Finally, after anaerobiosis of varying durations, room air is again introduced and the metabolic changes are followed as the nerve recovers.

We may turn our attention first to the graph of the galvanometer deflections which serve as an index of the functional condition of the nerve. This graph expresses the fact which was first discovered by von Baeyer (1903), that a nerve fails to conduct after being left for several hours in nitrogen. Asphyxia is preceded by a period of increased negative variation which may be due in part at least to a lowered threshold. The asphyxia time depends upon the condition of the frog and Frohlich (1904) has shown that nerves from well fed frogs maintain conduction for a longer time in nitrogen than those of starved frogs. This he interpreted as due to a more extensive store of reserve oxygen. Likewise, frogs taken directly from the stock kept in a cold room at 2 to 9°C could be asphyxiated only after 7 to 8 hours. After keeping the frogs for a few days at room temperature, however, this time was reduced to 2 or 3 hours and after 1 to 2 weeks, they could be asphyxiated in a little over 1 hour. When returned to the cold room the asphyxia time again increased. I do not know how long a nerve can be left in complete asphyxia without permanent injury. In this experiment the nerve was in nitrogen for 8½ hours and completely asphyxiated for 5½ hours, and recovery was about two-thirds or more complete upon renewed administration of oxygen. Frohlich tried the interesting experiment of exposing an asphyxiated nerve to oxygen for half a minute, then flushing out the oxygen with a vigorous stream of nitrogen. He then observed a partial recovery



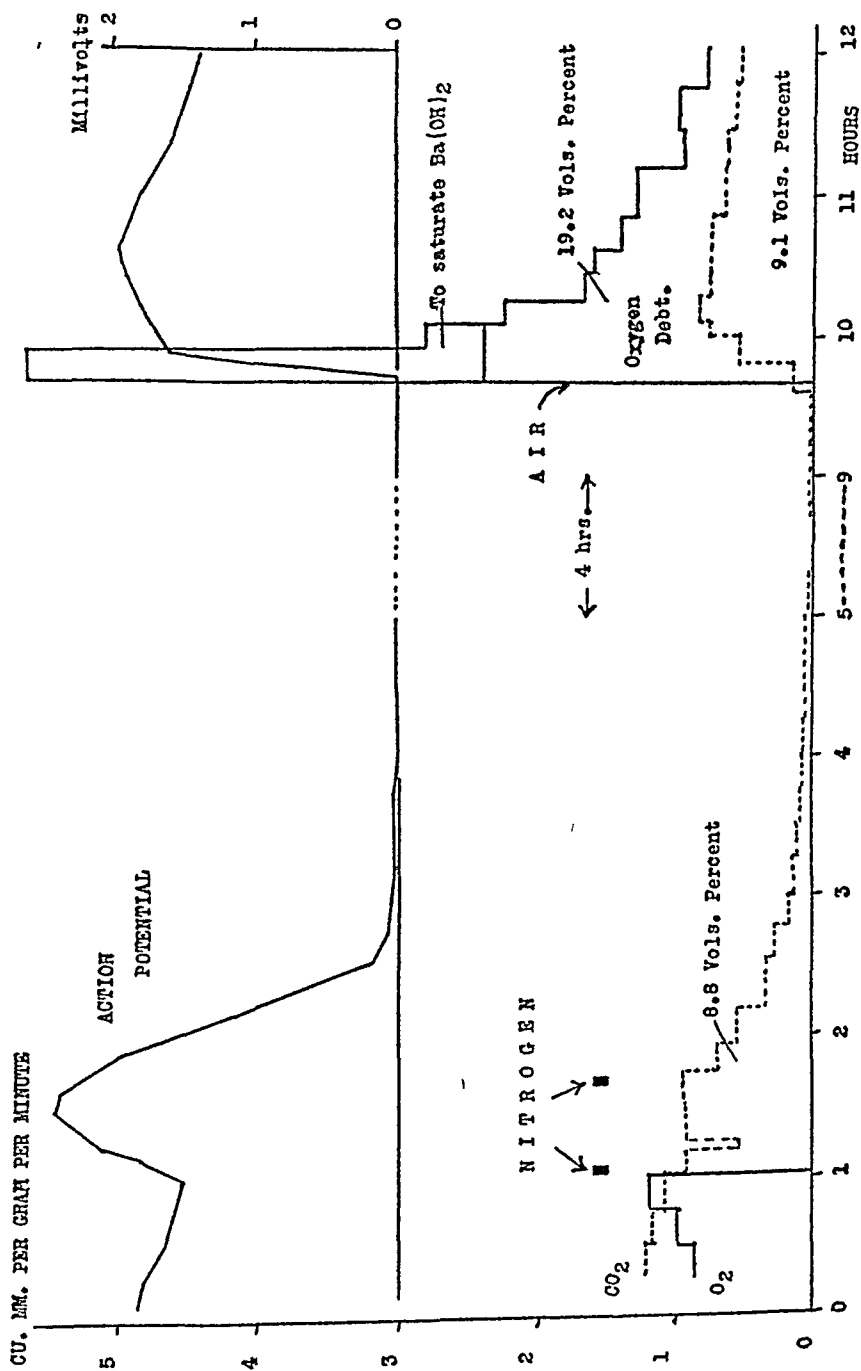


FIG 12 SIMULTANEOUS MEASUREMENTS OF THE OXYGEN CONSUMPTION, CARBON DIOXIDE, OUTPUT AND NEGATIVE VARIATION OF NERVES DURING ANAEROBIOSIS AND RECOVERY THEREFROM

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of function which required 32 minutes to disappear. Evidently the function depends upon something more than the tension of oxygen, for the oxygen which was able to diffuse into the nerve in half a minute should have diffused out again in a few minutes at least. It was perhaps combined at once in some relatively non-diffusible form. If the nerve had been 30 per cent saturated in half a minute this amount of oxygen would have been enough to last 10 to 20 minutes if none of it diffused out.

Another significant fact comes out of the work of Gottschalk (1920) who found that recovery can be made more complete by bathing the nerve in oxygenated Ringer's solution than by merely exposing it to an atmosphere of oxygen. This suggests the removal of diffusible waste products. It is a little difficult to reconcile with Gerard's statement, that a nerve fails no sooner in pure nitrogen than in oxygen-free Ringer's solution. Gottschalk, however, was led to the view that there was an accumulation of unoxidized waste products in nitrogen. Conduction could continue until such a concentration of these products was reached that further function was impossible. This view made the metabolism of nerve in activity resemble that of muscle.

The experiment in figure 12 seems to conform to this view. The measurements of the carbon dioxide output as shown in the dotted line indicates an anaerobic formation of 8.8 volumes per cent  $\text{CO}_2$ . The average anaerobic  $\text{CO}_2$  formation in 6 experiments was 8.6 volumes per cent. This is not far from the total  $\text{CO}_2$  content of a nerve exposed to zero  $\text{CO}_2$  tension and naturally suggests an anaerobic formation of lactic acid sufficient to liberate all the preformed bicarbonate. In this experiment as in all the others of this type which I have carried out, the conduction ceases when the carbon dioxide output becomes less than about 0.1 cu. mm. per gram per minute. This is true whether the conductivity persists for 1 hour or 5 hours and suggests some definite causal connection between the two. Presumably the lack of a suitable supply of energy occasions the loss of irritability.

Before discussing other possibilities we may press the analogy to muscle a little further and consider the metabolic response when air is readmitted. The readmission of air was accomplished in the same way that  $\text{CO}_2$  mixtures were introduced into the respirometer. The air to be introduced was previously contained in a bottle over sodium

hydroxide which was kept under water in the water bath. It was, therefore,  $\text{CO}_2$ -free and had the same temperature and vapor pressure as the gas inside the bottle. For 10 seconds the cocks to the respirometer were opened and this air was forced by displacement with mercury through the nerve chamber. 5 seconds later oxygen readings were resumed. Somewhat irregular results are sometimes obtained for the next 10 or 15 seconds but after that, control experiments show always the same movement, a gradual diminution of volume due to the greater solubility of oxygen than of nitrogen in barium hydrate.<sup>6</sup> The absolute magnitude of this volume shrinkage agrees fairly well (slightly larger if anything) with the calculated amount. It is complete in 20 to 30 minutes. When an asphyxiated nerve is contained in the bottle a similar shrinkage of volume occurs. In this experiment the shrinkage is so large that even after allowing for the saturation of the barium hydrate there remains a large excess oxygen consumption. Evidently the nerve has run up a considerable oxygen debt while in nitrogen. Over the period during which observations were made after exposure to nitrogen, the oxygen consumed was 19.2 volumes per cent and the carbon dioxide 9.1 volumes per cent. The oxygen debt was, therefore, 10.1 volumes per cent or 1.2 volumes per cent per hour. Gerard found an oxygen debt of 1.5 volumes per cent after 2 hours. The average of my experiments is 1 volume per cent per hour in nitrogen and about 2 volumes per cent per hour of complete asphyxia. According to the Pasteur or Meyerhof reaction this 19.2 volumes per cent of oxygen could cause the disappearance of the molecular equivalent of 38 volumes per cent of lactic acid as a maximum. Assuming that one-third of the lactic acid was neutralized by bicarbonate, we should expect a retention of 13 volumes per cent of carbon dioxide and we find a retention of 10 volumes per cent (19.2-9.1). This retention of  $\text{CO}_2$  is also about equal to the anaerobic  $\text{CO}_2$  output.<sup>7</sup>

<sup>6</sup> A second or third introduction of air in control experiments as in nerve experiments causes a small further diminution of volume of about 1 volume per cent.

<sup>7</sup> Certain other experiments of this series do not show this agreement between the oxygen debt and the anaerobic  $\text{CO}_2$ . If oxygen is readmitted immediately after asphyxia is complete the oxygen debt is much less while the anaerobic  $\text{CO}_2$  output is undiminished. After the delivery of this manuscript experiments were made on summer frogs showing smaller oxygen debts of only 1.5 to 3 volumes per cent, and not tending to increase with time. These large oxygen debts should be further confirmed.

of function which required 32 minutes to disappear. Evidently the function depends upon something more than the tension of oxygen, for the oxygen which was able to diffuse into the nerve in half a minute should have diffused out again in a few minutes at least. It was perhaps combined at once in some relatively non-diffusible form. If the nerve had been 30 per cent saturated in half a minute this amount of oxygen would have been enough to last 10 to 20 minutes if none of it diffused out.

Another significant fact comes out of the work of Gottschalk (1920) who found that recovery can be made more complete by bathing the nerve in oxygenated Ringer's solution than by merely exposing it to an atmosphere of oxygen. This suggests the removal of diffusible waste products. It is a little difficult to reconcile with Gerard's statement, that a nerve fails no sooner in pure nitrogen than in oxygen-free Ringer's solution. Gottschalk, however, was led to the view that there was an accumulation of unoxidized waste products in nitrogen. Conduction could continue until such a concentration of these products was reached that further function was impossible. This view made the metabolism of nerve in activity resemble that of muscle.

The experiment in figure 12 seems to conform to this view. The measurements of the carbon dioxide output as shown in the dotted line indicates an anaerobic formation of 8.8 volumes per cent  $\text{CO}_2$ . The average anaerobic  $\text{CO}_2$  formation in 6 experiments was 8.6 volumes per cent. This is not far from the total  $\text{CO}_2$  content of a nerve exposed to zero  $\text{CO}_2$  tension and naturally suggests an anaerobic formation of lactic acid sufficient to liberate all the preformed bicarbonate. In this experiment as in all the others of this type which I have carried out, the conduction ceases when the carbon dioxide output becomes less than about 0.1 cu. mm. per gram per minute. This is true whether the conductivity persists for 1 hour or 5 hours and suggests some definite causal connection between the two. Presumably the lack of a suitable supply of energy occasions the loss of irritability.

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Further evidence which strongly suggests an oxidative removal of lactic acid as an explanation of this oxygen debt is the fact that *the CO<sub>2</sub> output after asphyxia also passes through a definite maximum coinciding approximately with the oxygen maximum.*

The great discrepancy between the oxygen consumption and the carbon dioxide output after anaerobiosis can therefore be explained by a *storage of carbon dioxide* as lactic acid is removed. It could also be explained, however, by a *storage of oxygen*. This possibility was denied by the experiments of Winterstein (1907) on the spinal cord of the frog in which he found no change in the R Q when oxygen was readmitted to an asphyxiated nerve. In my experiments, however, there is an enormous change in the R Q at this time. Moreover, Gerard has brought forward convincing evidence that there is at least a small oxygen storage. His evidence on this important point is as follows. When the heat production is measured as the nerve is failing in nitrogen it is found that both the initial and the recovery heat diminish together, quite unlike the muscle in this respect, where the recovery heat diminishes at once but the initial heat persists. *Conduction and the recovery from conduction are therefore inseparable by nitrogen and since recovery is oxidative, conduction cannot take place without oxidation.*

In this connection Gerard and Meyerhof have shown clearly that anaerobic glycolysis will not suffice to maintain conduction in nerve. Thus by adding sugar to nerve they are able to maintain vigorous fermentation for several days. Although the energy turnover is ample, conduction remains suspended.

Conduction therefore necessitates oxidation. This, it seems to me, is the most fundamental fact now available concerning the metabolism of nerves. It is hard, therefore, to escape the conclusion that *some*, at least, of the oxygen debt is due to an oxidation reserve. Gerard and Meyerhof have offered less convincing evidence that *all* of the oxygen debt is due to an oxidation reserve. They find that lactic acid accumulates in the nerve in nitrogen but that analysis made in similar nerves exposed to nitrogen and then left in oxygen for 4 hours shows no diminution of lactic acid. Control nerves in oxygen alone show no accumulation of lactic acid. This is evidence against an oxidative removal of lactic acid. I doubt, however, whether these

authors would wish to exclude altogether the possibility of an oxidative removal of lactic acid on this evidence alone. Nor do I feel that their failure to find any increased  $\text{CO}_2$  content of nerves after recovery from asphyxia is altogether exclusive of this possibility. Gerard has also measured the carbon dioxide which is produced in nerve left for 20 hours in nitrogen and finds it to be 3 volumes per cent. This was about equal to the small oxygen debts which Gerard observed but it is hardly sufficient to explain an oxygen debt of 10 volumes per cent after only  $8\frac{1}{2}$  hours. I think it most probable that the excess oxygen over the carbon dioxide after asphyxia is due both to a storage of carbon dioxide by oxidative removal of lactic acid and to a storage of oxygen, or its equivalent.

According to Gerard's theory (1927, c) the same chemical processes should be involved in anaerobic conduction as in aerobic conduction, except that the oxidation is at the expense of something beside oxygen. We should expect, therefore, an extra output of carbon dioxide during stimulation in nitrogen. I have tried stimulating the nerve during the progress of asphyxia in experiments of the type illustrated in figure 12 but such stimulation seems to have no measurable effect upon the carbon dioxide output. Gerard and Meyerhof have tried to measure an increased lactic acid formation during stimulation in nitrogen by the differential manometer. This measurement depends upon the increased carbon dioxide liberated from bicarbonate by the lactic acid. The same result would be obtained from an increased carbon dioxide production by oxidation, but *none was found*. It should also be remarked that their failure to detect an increased lactic acid in this way does not prove that lactic acid formation does not account for the initial heat in nerve—a possibility which Gerard admits—for the lactic acid equivalent of the initial heat is less than their stated experimental error. The  $\text{CO}_2$  equivalent of the total heat should, however, be measurable, though small, since the fibres are failing.

The graphs in figure 13 represent a comparison between the rates of diffusion of carbon dioxide into a nerve, as shown by the black dots, and the rate of recovery from asphyxia, as shown by the three curves marked with circles. The moment of admission of oxygen to an asphyxiated nerve is, in fact, a dramatic moment.  $1\frac{1}{2}$  to 2 minutes



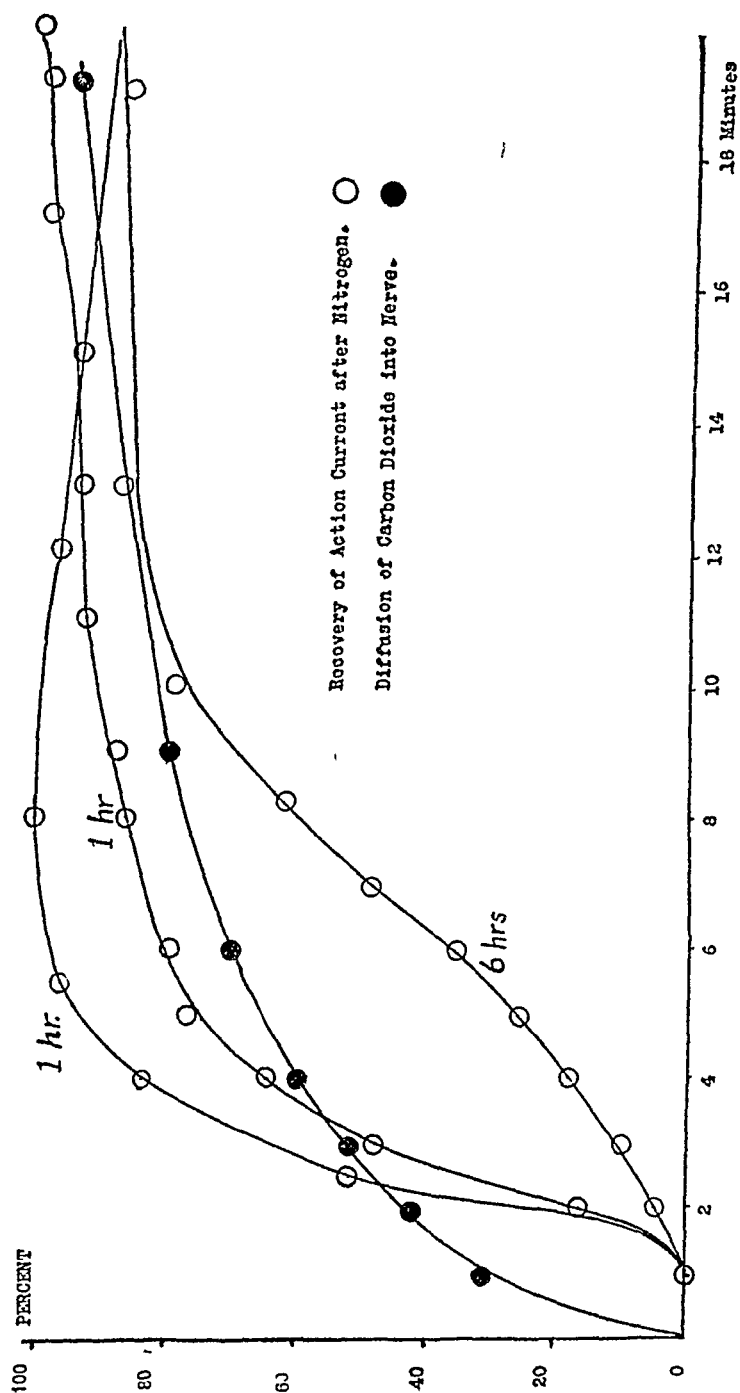


FIG 13 A COMPARISON BETWEEN THE RATE OF DIFFUSION OF CARBON DIOXIDE INTO A NERVE AND THE RATE OF RECOVERY OF SIMILAR NERVES FROM ASPHYXIA WHEN OXYGEN IS ADMITTED, AFTER VARYING INTERVALS OF COMPLETELY SUSPENDED CONDUCTION (1 TO 6 HOURS)

after exposure to oxygen, conduction begins to return and in a few more minutes it is complete. The resulting curve is, therefore, slightly S-shaped. After 8 hours in nitrogen, as shown in the lower curve, the recovery is considerably slower (as Gerard has also observed) and is, in fact, much less complete. Oxygen would saturate a nerve somewhat more quickly than would carbon dioxide, so it appears not only that diffusion is rapid enough to account for the rate of recovery observed, but also that at least after not too long a time in nitrogen, recovery may occur very promptly after oxygen has reached an asphyxiated fibre.

In conclusion, I must apologize for failure to do justice to many aspects of this subject, merely because they did not happen to fit into the particular scheme of this lecture. I have dwelt at unnecessary length upon some of the relatively unimportant details of the phenomena described. I have spent time in describing new methods of investigation adapted to this subject. Finally, I have tried to outline the essential features of the energy cycle of nerves in activity, as they are known today, the point being that in nervous transmission, unlike muscular contraction, oxidation is a necessary accompaniment. The evidence for this important point from the heat measurements of Gerard seems to me very difficult to interpret in any other way. The evidence from measurements of lactic acid,  $\text{CO}_2$  and oxygen is still, it seems, incomplete. I only regret that those who are more particularly responsible for this information could not have been here to expound more fittingly their own important contributions to this very immature subject.

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